

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S DEPOSITION DESIGNATIONS AND COUNTER DESIGNATIONS  
FOR CAROL MEYER**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached deposition designations and counter-designations for the May 22, 2007 deposition of Carol Meyer, former Operations Manager, Senior Operations Manager, Head of the Clinical Program, Anti-Infective Venture (ABT-773).

Dated: February 18, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By:   /s/ Eric J. Lorenzini    
Eric J. Lorenzini

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**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

\_\_\_\_\_  
/s/ Ozge Guzelsu



**Carol Meyer Deposition Designations**

<b>Depo Date</b>	<b>Witness</b>	<b>Hancock Designation</b>	<b>Abbott Counter Designation</b>	<b>Abbott Designation</b>	<b>Deposition Exhibit</b>	<b>Plaintiff Exhibit</b>	<b>Defendant Exhibit</b>
05/22/07	Meyer, Carol	28:4-28:16	28:17-29:3		1	HV	
05/22/07	Meyer, Carol	30:8-30:16	29:21-30:7				
05/22/07	Meyer, Carol	30:8-30:16	30:17-30:23				
05/22/07	Meyer, Carol	31:9-31:22	30:24-31:8				
05/22/07	Meyer, Carol	31:9-31:22	31:23-32:16				
05/22/07	Meyer, Carol	38:5-38:8	35:18-38:4				
05/22/07	Meyer, Carol	38:5-38:8	38:9-38:14				
05/22/07	Meyer, Carol	38:15-38:21	38:22-39:4				
05/22/07	Meyer, Carol	40:4-40:8	39:5-40:3				
05/22/07	Meyer, Carol	40:4-40:8	40:9-41:2				
05/22/07	Meyer, Carol	41:3-42:2	No Counter		3	HW	
05/22/07	Meyer, Carol	42:14-43:2			3	HW	
05/22/07	Meyer, Carol	44:4-44:21	44:22-45:24		4	HZ	
05/22/07	Meyer, Carol	54:19-55:3	52:10-54:18				
05/22/07	Meyer, Carol	54:19-55:3	55:4-55:21				
05/22/07	Meyer, Carol	55:22-56:18	56:19-58:2		5	IF	
05/22/07	Meyer, Carol	58:3-58:20	57:22-58:2				
05/22/07	Meyer, Carol	59:8-60:5	60:6-61:19		5	IF	
05/22/07	Meyer, Carol	63:17-63:23	63:9-63:16				
05/22/07	Meyer, Carol	64:2-64:22	64:23-65:14		5	IF	
05/22/07	Meyer, Carol	65:15-66:16	66:17-67:1		6	IG	
05/22/07	Meyer, Carol	67:19-68:3	67:2-67:18		6	IG	
05/22/07	Meyer, Carol	67:19-68:3	68:4-68:18				
05/22/07	Meyer, Carol	69:16-70:4	69:11-69:15		6	IG	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
05/22/07	Meyer, Carol	73:5-73:9	72:13-73:4		6	IG	
05/22/07	Meyer, Carol	73:21-74:1	73:10-73:20		6	IG	
05/22/07	Meyer, Carol	76:20-77:13	77:14-77:17		7	II	
05/22/07	Meyer, Carol	81:8-81:22	No Counter		8	IL	
05/22/07	Meyer, Carol	85:15-86:3	85:10-85:14		8	IL	
05/22/07	Meyer, Carol	85:15-86:3	86:4-86:7				
05/22/07	Meyer, Carol	87:17-88:9	88:10-89:17		9	IO	
05/22/07	Meyer, Carol	90:14-91:5	No Counter		9	IO	
05/22/07	Meyer, Carol	91:16-92:5	91:6-91:15		9	IO	
05/22/07	Meyer, Carol	94:17-94:23	93:15-94:16		9	IO	
05/22/07	Meyer, Carol	94:17-94:23	94:24-95:4				
05/22/07	Meyer, Carol	98:23-99:8	98:13-98:22		9	IO	
05/22/07	Meyer, Carol	98:23-99:8	99:9-100:14				
05/22/07	Meyer, Carol	100:16-101:14	101:15-101:18		10	IN	
05/22/07	Meyer, Carol	102:2-102:12	102:13-102:20		10	IN	
05/22/07	Meyer, Carol	111:18-112:14	109:15-110:1		11	IR	
05/22/07	Meyer, Carol	114:23-115:6	112:19-114:22		11	IR	
05/22/07	Meyer, Carol	114:23-115:6	115:7-115:13				
05/22/07	Meyer, Carol	115:14-115:17	No Counter		12	IQ	
05/22/07	Meyer, Carol	117:18-118:16	No Counter		12	IQ	
05/22/07	Meyer, Carol	127:6-127:9	No Counter		15	IM	
05/22/07	Meyer, Carol	129:15-130:1	128:2-129:14		15	IM	
05/22/07	Meyer, Carol	131:15-132:8	130:2-131:14		15	IM	
05/22/07	Meyer, Carol	133:10-133:19					



## **Color Key to Deposition Designations**

 **Designation by Plaintiffs**

 **Counter Designation by Defendants**

 **Designation by Defendants**



Meyer, Carol (Linked) 5/22/2007 9:00:00 AM

1 UNITED STATES DISTRICT COURT  
2 FOR THE DISTRICT OF MASSACHUSETTS

3

4 JOHN HANCOCK LIFE INSURANCE )  
5 COMPANY, JOHN HANCOCK VARIABLE )  
6 LIFE INSURANCE COMPANY and )  
7 MANULIFE INSURANCE COMPANY )  
8 (f/k/a INVESTORS PARTNER )  
9 INSURANCE COMPANY), )

10 Plaintiffs, ) Civil Action No.

11 -vs- ) 05-11150-DPW

12 ABBOTT LABORATORIES, )

13 Defendant. )

14

15

16

17 THE VIDEOTAPED DEPOSITION OF  
18 CAROL SUSAN MEYER

19

20 May 22, 2007

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24



Meyer, Carol (Linked) 5/22/2007 9:00:00 AM

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The videotaped deposition of  
CAROL SUSAN MEYER, called by the Plaintiffs for  
examination, taken pursuant to the Federal Rules of  
Civil Procedure of the United States District  
Courts pertaining to the taking of depositions,  
taken before CORINNE T. MARUT, C.S.R. No. 84-1968,  
a Notary Public within and for the County of  
DuPage, State of Illinois, and a Certified  
Shorthand Reporter of said state, at the offices of  
Levenfeld Pearlstein, Suite 1300, Two North LaSalle  
Street, Chicago, Illinois, on the 22nd day of May,  
A.D. 2007, commencing at 9:00 a.m.

Meyer, Carol (Linked) 5/22/2007 9:00:00 AM

1 PRESENT:

2 CHOATE, HALL & STEWART LLP,

3 (Two International Place,

4 Boston, Massachusetts 02110,

5 617-248-5000), by:

6 MR. JOSEPH H. ZWICKER,

7 jzwicker@choate.com,

8 appeared on behalf of the Plaintiffs;

9

10 MUNGER, TOLLES & OLSON LLP,

11 (355 South Grand Avenue, 35th Floor,

12 Los Angeles, California 90071-1560,

13 213-683-9276), by:

14 MS. ÖZGE GÜZELSU,

15 ozge.guzelsu@mto.com,

16 appeared on behalf of the Defendant.

17

18 VIDEOTAPED BY:

19 JOE ELSEY,

20 Esquire Deposition Services.

21

22

23 REPORTED BY: CORINNE T. MARUT, C.S.R. No. 84-1968

24

Meyer, Carol (Linked) 5/22/2007 9:00:00 AM

1 MS. GÜZELSU: Objection.

2 BY THE WITNESS:

3 A. Yes.

4 (WHEREUPON, a certain document was

5 marked Meyer Deposition Exhibit

6 No. 1, for identification, as of

7 05-22-2007.)

8 MR. ZWICKER: Before the witness is Meyer

9 Exhibit No. 1, which is a series of e-mails with

10 bearing Bates No. ABBT 305783.

11 BY MR. ZWICKER:

12 Q. Ms. Meyer, if you don't mind, would you

13 look at the bottom e-mail first, which is the one

14 from Keith Hendricks to various persons, and let me

15 know when you're done.

16 A. Okay.

17 Q. You were a member of the core team for

18 773 in March of 2000, weren't you?

19 A. Yes.

20 Q. Does reviewing this document cause you

21 to conclude that DSG activities for 773 began in

22 2000 and not 2001? The date of the e-mail is

23 March 16, 2000.

24 A. Since I wasn't copied on this, obviously

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1 it's not something I was aware of at that time.

2 This wasn't sent to me and I wasn't included as a  
3 team member. So, I -- just based on the date.

4 Q. Keith Hendricks writes in part -- this  
5 is the first sentence of the e-mail -- "Greetings.  
6 We now need to turn our attention to the very  
7 important task of formulating the dosing strategy  
8 for ABT-773."

9 Now I'm reading the next paragraph.

10 A. Um-hmm.

11 Q. "As we discussed in our last meeting,  
12 the timetable for completing this assessment will  
13 be tight." So it must certainly -- "so it will  
14 most certainly require calendar prioritization from  
15 all of us. But as we also discussed, there is no  
16 more important issue for us to make a decision on  
17 right now in our entire portfolio, so the time will  
18 be well spent."

19 Do you see that?

20 A. Yes.

21 Q. And I appreciate you're not on this  
22 e-mail. But based on your work on 773 in 2000 and  
23 2001, do you agree with Mr. Hendricks' assessment  
24 that the dosing decision for 773 is one of the most

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1 important decisions in Abbott's entire portfolio?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. Since I only work on the one -- worked

5 on the one project, I would not have access to that

6 information.

7 BY MR. ZWICKER:

8 Q. That's a fair answer. Let me ask you a

9 different question.

10 Based on your work just on 773, do you

11 agree with the proposition that the dosing decision

12 for 773 was the most important decision relating to

13 the development of 773?

14 A. For any drug in development, we would

15 have been in Phase II, that is the most important

16 decision.

17 Q. What --

18 A. But that applies to every drug.

19 Q. I'm sorry.

20 A. Sorry.

21 Q. The dosing decision applies to every

22 drug?

23 A. Yeah. In Phase II you do dose ranging.

24 Q. What did you understand the dosing



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1 decision for 773 to be?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. You know, based on our target product  
5 profile, we wanted something that was convenient  
6 and that would compete with other drugs in the  
7 marketplace.

8 BY MR. ZWICKER:

9 Q. And a target profile that maximized  
10 convenience would have 773 dosed at once a day  
11 rather than twice a day, correct?

12 A. That would definitely be our preference.

13 MS. GÜZELSU: Objection. Sorry. Go ahead.

14 BY MR. ZWICKER:

15 Q. If you could finish your answer.

16 A. That would be our preference.

17 Q. Why would that be your preference?

18 A. Because drugs on the market are dosed  
19 once a day already for the same indications.

20 Q. So, there would be a significant  
21 commercial advantage to once-a-day dosing. Was  
22 that your understanding?

23 MS. GÜZELSU: Objection.

24 BY THE WITNESS:

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1 A. Yes, there's -- there's commercial  
2 advantages for once-a-day dosing.

3 BY MR. ZWICKER:

4 Q. Did there come a time when you  
5 understood how significant those commercial  
6 advantages were?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. Having worked in the field of  
10 anti-infectives, I knew that once-a-day dosing is  
11 desirable.

12 BY MR. ZWICKER:

13 Q. Because of the impact on sales,  
14 potential sales?

15 A. Because of the impact on compliance by  
16 patients.

17 Q. What about the impact on the value of  
18 the product?

19 A. If you had the choice to take a  
20 once-a-day drug versus a twice-a-day, it would be  
21 highly more valuable for a drug that's dosed once a  
22 day.

23 Q. Would you agree with the proposition  
24 that what you said is true because a patient is

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1 Phase II. So, it would have been sometime in the  
2 summer of 2000.

3 BY MR. ZWICKER:

4 Q. Do you recall that Dr. Leiden made the  
5 decision in July 2001 to proceed with BID dosing  
6 for certain indications for 773?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. The team may have made a recommendation  
10 based on looking at where we were in the  
11 development program that it made more sense to move  
12 forward with BID for certain indications. More  
13 severe.

14 BY MR. ZWICKER:

15 Q. Do you recall that was in July of 2001,  
16 thereabouts?

17 A. Thereabouts.

18 MR. ZWICKER: Let's mark this as No. 2.

19 (WHEREUPON, a certain document was

20 marked Meyer Deposition Exhibit

21 No. 2, for identification, as of

22 05-22-2007.)

23 MR. ZWICKER: Before the witness is Meyer

24 Exhibit No. 2, which is an August 1999 project



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1 status report for ABT-773.

2 BY MR. ZWICKER:

3 Q. Ms. Meyer, would you take a look at it

4 and let me know when you're done.

5 All set?

6 A. Okay.

7 Q. Do you recognize the form of

8 Exhibit No. 2?

9 A. Yes, I do.

10 Q. Is this the kind of document that you

11 would draft?

12 A. Yes.

13 Q. Based on input from others?

14 A. Yes.

15 Q. Take a look at page 2 where it says

16 "Drug Safety." Actually it bears Bates

17 No. ABBT 4628.

18 A. Um-hmm.

19 Q. Do you see the portion that says

20 "Drug Safety"?

21 A. Yes, I do.

22 Q. Is that something you wrote?

23 A. I don't recall if I wrote it or if the

24 team member provided it to me and I entered it.

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1 Q. The first column says, "QD dosing may  
2 not be feasible due to less than 50 percent  
3 relative bioavailability with ER compared to IR.

4 Market share impact of QD dosing is high."

5 Do you know what ER is?

6 A. Extended release.

7 Q. And IR?

8 A. Immediate release.

9 Q. Do you recall based on your work on 773  
10 in the 1999 time period that you understood that  
11 there were obstacles to QD dosing based on the  
12 speed at which 773 was absorbed in the body?

13 A. Yes.

14 Q. What was your understanding of those  
15 obstacles?

16 A. To be honest, you know, I'm not a  
17 scientist; and while I would have been very  
18 cognizant of the issues in 1999, I don't recall all  
19 the details now.

20 Q. Did you have discussions with other  
21 persons on the 773 team -- well, let me strike  
22 that.

23 This issue was called pharmacokinetics,  
24 is that right?

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1 A. That's correct.

2 Q. Did you have discussions with other  
3 persons on the 773 team regarding pharmacokinetics?

4 A. Yes.

5 Q. Based on those discussions did you have  
6 an understanding in 1999 that pharmacokinetics  
7 could be an obstacle to once-a-day dosing?

8 A. Yes.

9 Q. A significant obstacle?

10 A. We hadn't done studies enough in  
11 patients to know that.

12 Q. So, it was uncertain?

13 A. As every drug in Phase I is uncertain  
14 about dosing.

15 Q. So, in other words, you couldn't say one  
16 way or another whether once-a-day dosing would be  
17 likely or unlikely?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. Until you dose actual patients, you  
21 don't know that answer.

22 BY MR. ZWICKER:

23 Q. At what point were patients -- were  
24 patients dosed with once-a-day versus twice-a-day



1 dosing? Do you know at what point in time?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. During Phase II.

5 BY MR. ZWICKER:

6 Q. Based on your work on 773 did you come

7 to understand the term "resistance claim"?

8 A. Yes.

9 Q. What was your understanding of what a

10 resistance claim was?

11 A. It would be a label claim that the drug

12 is effective against resistant pathogens.

13 Q. For 773 what resistant pathogens was

14 Abbott seeking a resistance claim for?

15 A. Penicillin-resistant Strep pneumo and

16 macrolide-resistant Strep pneumo.

17 Q. What was your understanding about why,

18 based on your work on 773, Abbott wanted a

19 resistance claim against penicillin-resistant and

20 macrolide-resistant Strep pneumo?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. Again, I'm not a scientist, but

24 developing resistance to pathogens isn't a good

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1 thing for patients who have respiratory tract  
2 infections. They won't respond to antibiotics.

3 BY MR. ZWICKER:

4 Q. Was it your understanding, then, that  
5 the -- that achieving a resistance claim would help  
6 differentiate 773 from other products on the  
7 market?

8 A. Yes.

9 Q. How?

10 A. Because there are very few anti- --  
11 antibiotics on the market with resistance claims.

12 Q. Did you understand based on your work on  
13 773, and let's take the period in 2000 and early  
14 2001, that achieving a resistance claim would help  
15 increase Abbott's likelihood of obtaining FDA  
16 approval for 773?

17 A. Again, I'm not the regulatory expert.  
18 Abbott's likelihood for approval would be based on  
19 safety and efficacy of the drug and profile  
20 compared to, you know, drugs available.

21 So, resistance claim is one aspect but  
22 not the only one.

23 Q. So, is it your understanding that a  
24 resistance claim could be a factor that assists

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1 Abbott in obtaining regulatory approval?

2 A. It may be a factor, yes.

3 (WHEREUPON, a certain document was

4 marked Meyer Deposition Exhibit

5 No. 3, for identification, as of

6 05-22-2007.)

7 MR. ZWICKER: Before the witness is Meyer

8 Exhibit No. 3, which is titled "2000 Strategic

9 Marketing Plan, June 2000," and it has Bates

10 numbers 570747 through 770.

11 BY MR. ZWICKER:

12 Q. Ms. Meyer, could you look at this

13 document and let me know if you recognize it.

14 A. I don't recall this document, but some

15 of the sections would have been used in my

16 development plan. So, some of these sections are

17 familiar, but the document itself is not familiar.

18 Q. When you say "development plan," what

19 are you talking about?

20 A. There is a development plan document.

21 Q. For 773?

22 A. Yes.

23 Q. That you wrote?

24 A. Yes. There were contributors and Rod



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1 was a contributor.

2 Q. Turn to page 16 where it says "Key

3 Commercial Issues & Opportunities. Issue" -- where

4 it says "A. Issues. Issue No. 1. Uncertainty in

5 ABBT convenience profile, i.e., potential BID

6 dosing." (As read.)

7 A. Um-hmm.

8 Q. Do you see that?

9 A. Yes.

10 MS. GÜZELSU: Objection. It's "ABT-773

11 convenience profile." Sorry.

12 MR. ZWICKER: Thank you.

13 BY MR. ZWICKER:

14 Q. Based on your work on 773, did you agree

15 that the -- the most significant uncertainty for

16 773 was whether it could be dosed once a day or

17 twice a day?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. It was one of the, you know, significant

21 components of the target product profile.

22 BY MR. ZWICKER:

23 Q. And Abbott was uncertain whether 773

24 could be dosed once a day or twice a day, correct?

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1 A. Until we dosed patients, we would be  
2 uncertain, correct.

3 Q. Turn to page 11 where it says  
4 "Competitive Analysis."

5 A. Yes.

6 Q. The one, two -- third paragraph begins,  
7 "Macrolides are regarded as extremely safe and  
8 efficacious agents, but resistance to these agents,  
9 particularly with Strep pneumoniae, is becoming  
10 more widespread."

11 Do you see that?

12 A. Yes.

13 Q. As between a resistance claim between --  
14 for penicillin-resistant Strep pneumoniae and  
15 macrolide-resistant Strep pneumoniae, based on your  
16 understanding which one was more important for  
17 Abbott?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. Honestly I wouldn't know enough to make  
21 the differentiation.

22 BY MR. ZWICKER:

23 Q. Did you think both were significant  
24 based on your work on 773?



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1 MS. GÜZELSU: Objection.

2 BY THE WITNESS:

3 A. Yes, they'd both be significant.

4 (WHEREUPON, a certain document was

5 marked Meyer Deposition Exhibit

6 No. 4, for identification, as of

7 05-22-2007.)

8 MR. ZWICKER: Before the witness is Meyer

9 Exhibit No. 4, which is a document bearing Bates

10 Nos. ABBT 557552 through 557. It is an e-mail and

11 covering document.

12 BY MR. ZWICKER:

13 Q. Ms. Meyer, would you take a look at

14 Exhibit No. 4 and let me know if you recognize it.

15 A. Yes, I recognize it.

16 Q. What is it?

17 A. It's the regulatory SWOT analysis for

18 the development plan.

19 Q. And this is the development plan that

20 you worked on?

21 A. Correct.

22 Q. Did you write the regulatory strategy

23 for the development plan?

24 A. No, I did not.

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1 Q. Who did?

2 A. It would have been a combination of

3 Abbott International regulatory and U.S.

4 regulatory.

5 Q. So, some combination of Jeanne Fox and

6 Greg Bosco and others?

7 A. They would represent U.S. regulatory.

8 Q. Who represented international?

9 A. Nigel Livesey and Jennifer Moore.

10 Q. Do you know why Greg Bosco provided the

11 regulatory analysis to you for review?

12 A. Because I'm responsible for the overall

13 document.

14 Q. And when he provided it to you, would

15 you review it?

16 A. Yes.

17 Q. And if you had questions, would you ask

18 them?

19 A. Yes.

20 Q. So, you felt comfortable enough with the

21 regulatory issues to ask questions of the people

22 that wrote the document. Fair?

23 A. It needed to fit in the overall plan,

24 yes.

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1 THE WITNESS: Go ahead.

2 MS. GÜZELSU: Objection.

3 BY MR. ZWICKER:

4 A. FDA would have concerns about liver  
5 enzyme increases for any drug metabolized by the  
6 liver.

7 BY MR. ZWICKER:

8 Q. Including 773?

9 A. Yes.

10 Q. Do you remember participating in a  
11 teleconference with the FDA November of 2000 where  
12 the FDA put 773's Phase III clinical trials on  
13 hold?

14 A. I did not participate in that  
15 teleconference.

16 Q. Did there come a time when you learned  
17 about it?

18 A. Yes.

19 Q. How did you learn about it?

20 A. Most likely through a conversation with  
21 Jeanne Fox or Greg Bosco.

22 Q. What did they tell you?

23 A. The outcome of the conversation. There  
24 was some definite misunderstandings because FDA had



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1 moved our meeting multiple times and we had  
2 informed them we were going to start the Phase III  
3 studies, and there was misunderstanding with the  
4 FDA reviewers as to the fact that we had already  
5 started.

6 Q. Do you remember learning from Jeanne Fox  
7 or someone else that the FDA was dissatisfied with  
8 the -- the toxicology studies that Abbott had  
9 performed relating to QT prolongation?

10 MS. GÜZELSU: Objection.

11 BY THE WITNESS:

12 A. I can't say whether they were  
13 dissatisfied. They were looking for some  
14 additional studies that they would like us to do.

15 BY MR. ZWICKER:

16 Q. Do you recall being surprised that the  
17 FDA had asked for additional toxicology work?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. I don't recall being surprised.

21 BY MR. ZWICKER:

22 Q. You expected it?

23 A. It's standard fare at that early phase  
24 that there be potential requests for other

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1 non-clinical or preclinical animal studies.

2 Q. Do you recall persons other than you

3 being surprised by the FDA's request?

4 A. I think we weren't surprised. I think

5 it was more related to the fact that they wanted

6 studies in dog.

7 Q. What about the fact that they wanted

8 studies in dog that caused concern --

9 MS. GÜZELSU: Objection.

10 BY MR. ZWICKER:

11 Q. -- by persons you worked with?

12 A. Basically we had already shown evidence

13 that the dog would vomit the drug and wouldn't get

14 enough blood levels to actually evaluate it

15 appropriately.

16 So, it didn't appear that FDA was

17 reading and reviewing our data thoroughly enough to

18 understand that.

19 Q. Based on what you learned about the

20 November 20th meeting, were you concerned that the

21 FDA had set a high hurdle for Abbott to convince it

22 that 773 was safe for the heart?

23 MS. GÜZELSU: Objection.

24 BY THE WITNESS:



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1 A. The hurdles for any antibiotic in this  
2 type of population are extremely high and we knew  
3 that that would be a high hurdle.

4 BY MR. ZWICKER:

5 Q. Were you, personally speaking, uncertain  
6 whether you could satisfy the FDA's concerns  
7 regarding 773 in 2000?

8 MS. GÜZELSU: Objection.

9 BY THE WITNESS:

10 A. Personally?

11 BY MR. ZWICKER:

12 Q. Yeah, your own view.

13 A. I don't think at that time we saw any --  
14 we were taking every precaution. Adding the EKG  
15 monitoring in Phase III, we felt we were obtaining  
16 above and beyond what would be required to satisfy  
17 their concerns.

18 Q. But, of course, you couldn't be certain  
19 that you would ultimately satisfy them. Fair?

20 A. We hadn't done the studies yet. So, it  
21 was a question we were all going to be answering.

22 (WHEREUPON, a certain document was

23 marked Meyer Deposition Exhibit

24 No. 5, for identification, as of

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1 05-22-2007.)

2 MR. ZWICKER: Before the witness is Meyer

3 Exhibit No. 5, which is an e-mail from Jeanne Fox

4 dated November 28, 2000 to various persons

5 including Carol Meyer and it has Bates No. 558150.

6 BY MR. ZWICKER:

7 Q. Ms. Meyer, would you review

8 Exhibit No. 5 and tell me if you recognize it.

9 A. Yes.

10 Q. What is it?

11 A. It's basically the outcome of a

12 teleconference with FDA.

13 Q. Did you participate in that conference

14 with the FDA?

15 A. I must have because it says in here that

16 I was there.

17 Q. Do you remember it?

18 A. Frankly, no.

19 Q. Well, read the document in its entirety

20 and I'll ask you a few questions --

21 A. Okay.

22 Q. -- to see if it refreshes your

23 recollection.

24 A. Okay.

1 Q. Do you recall that at the November 27 --

2 well, strike that.

3 You know what an End of Phase II meeting

4 is, correct?

5 A. Yes.

6 Q. What is it?

7 A. It's a meeting with the regulatory

8 agency to review results of our Phase II studies

9 and plans for Phase III.

10 Q. And is Abbott's hope or your hope for an

11 End of Phase II meeting that the FDA will provide

12 Abbott some guidance regarding how the Phase III

13 trial should proceed?

14 A. They'll provide their input as to

15 whether or not what we've proposed is adequate and

16 any issues that they have that we need to address.

17 Q. Fair to say that in your experience at

18 Abbott that Abbott took End of Phase II meetings

19 and the advice given by the FDA at those meetings

20 seriously?

21 A. Yes.

22 Q. At the End of Phase II meeting which

23 took place on November 27, Abbott told the FDA that

24 it would seek a resistance claim for 773, is that



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1 right?

2 A. Yes.

3 Q. What was the FDA's response to Abbott's

4 notice that it would seek a resistance claim for

5 773?

6 A. They needed a good solid body of

7 evidence.

8 Q. What did you understand that to mean?

9 A. It's one of those things where based on

10 the data package we'd submit they would decide if

11 it was adequate or not, but they wouldn't

12 pre-define it.

13 Q. The data package that Abbott would

14 submit would consist of some number of isolates.

15 Is that fair?

16 A. For the resistance claim, yes.

17 Q. And this would be the resistance claim

18 for both penicillin-resistant and

19 macrolide-resistant *Strep pneumoniae*?

20 A. That's correct.

21 Q. And the package that Abbott would submit

22 would contain as well eradication data for those

23 isolates, wouldn't it?

24 MS. GÜZELSU: Objection.

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1 BY THE WITNESS:

2 A. I don't recall exactly how they'd  
3 present the data. But, yes, you'd have to show  
4 that you eradicated the pathogen.

5 BY MR. ZWICKER:

6 Q. Or some number of them?

7 A. Right.

8 Q. The next sentence -- well, strike that.

9 In the middle paragraph of the second  
10 paragraph of Exhibit 5 says, "They cautioned us  
11 that they have not seen a body of data that  
12 supports macrolide-resistant *Strep pneumoniae* as a  
13 clinical concern."

14 Do you see that?

15 A. Yes.

16 Q. What does that mean?

17 A. Working in the anti-infective community,  
18 most of the data supporting resistance *Strep pneumo*  
19 is in vitro meaning it's done in Petri dishes.

20 So, again, it's the precursor to having  
21 a huge clinical body of knowledge that patients are  
22 failing antibiotics because of resistance.

23 Q. So, is it fair to say that what the FDA  
24 is telling you is they haven't seen from a clinical

1 standpoint a sufficient number of patients that  
2 actually have macrolide-resistant Strep pneumoniae?

3 MS. GÜZELSU: Objection.

4 BY THE WITNESS:

5 A. My -- that would be my assumption.

6 BY MR. ZWICKER:

7 Q. And is the FDA also telling you that  
8 they haven't seen data showing that -- well, strike  
9 that.

10 So, did you come away from the meeting  
11 on the 27th with the understanding that you would  
12 have to convince the FDA that there was such a  
13 thing as macrolide-resistant Strep pneumoniae?

14 MS. GÜZELSU: Objection.

15 BY THE WITNESS:

16 A. Based on the fact that there was only I  
17 think one other drug on the market that had a  
18 resistance claim and it was a growing potential  
19 problem moving forward, that, yes, it would be  
20 challenging.

21 BY MR. ZWICKER:

22 Q. It would be challenging to convince the  
23 FDA that there was such a thing as  
24 macrolide-resistant Strep pneumoniae, right.



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1 MS. GÜZELSU: Objection.

2 BY THE WITNESS:

3 A. It's not challenging from an in vitro  
4 standpoint. But when you -- you know, you're  
5 looking for clinical failures and, you know, that  
6 would be challenging.

7 BY MR. ZWICKER:

8 Q. It would be challenging from a clinical  
9 standpoint?

10 A. Correct.

11 Q. And you would also have to show the FDA,  
12 assuming you could show there was such a thing as  
13 macrolide-resistant Strep pneumoniae, that 773 was  
14 efficacious against it, correct?

15 A. We had data that showed that it was  
16 efficacious in vitro.

17 Q. But not in clinical trials?

18 A. Nobody has a lot of data in clinical  
19 trials. We hope nobody has resistant Strep pneumo.

20 Q. Zithromax is a macrolide, right?

21 A. Correct.

22 Q. The next sentence says, "They also  
23 advised us that we would need to include bacteremic  
24 CAP patients with resistant pathogens in order to

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1 A. If there is severe patients, you would  
2 want to maybe treat them initially with something  
3 more potent.

4 Q. Like an IV formulation?

5 A. Yes. But not impossible.

6 Q. Not impossible to treat them with an  
7 oral formulation?

8 A. Correct.

9 Q. Did you come away from the November 27  
10 End of Phase II meeting with the belief that Abbott  
11 would need an IV formulation to achieve a  
12 resistance claim?

13 A. No.

14 Q. Why not?

15 A. Because you can do the same with the  
16 tablet formulation.

17 Q. Did you come away from the November 27  
18 meeting with an understanding that it would be --  
19 that it would advance the likelihood of achieving a  
20 resistance claim if Abbott had an IV formulation?

21 A. Certainly it would round out the  
22 portfolio for the compound to have an IV  
23 formulation, yes.

24 Q. That it would be beneficial?

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1 A. Yes.

2 Q. Did you come away from the November 27

3 End of Phase II meeting with the understanding that

4 Abbott had an uphill fight to convince the FDA to

5 grant a resistance claim for 773?

6 MS. GÜZELSU: Objection.

7 BY THE WITNESS:

8 A. Every drug development compound is an

9 uphill fight. It's a huge amount of work to get to

10 a regulatory application. So, this would be just

11 like any other drug development project.

12 BY MR. ZWICKER:

13 Q. But specifically given the FDA's concern

14 about whether there was such a thing as

15 macrolide-resistant Strep pneumoniae, did you

16 personally believe that Abbott's hurdle was

17 particularly high?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. Abbott's hurdle was particularly high

21 because of the population you treat with

22 antibiotics.

23 BY MR. ZWICKER:

24 Q. How do you mean?



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1 A. The majority of patients other than a  
2 respiratory tract infection are healthy, you know,  
3 healthy individuals. So, there is no major  
4 underlying disease.

5 Q. How did that affect how difficult it  
6 would be to obtain a resistance claim?

7 A. The drugs need to be extremely safe and  
8 effective.

9 Q. Would you say the FDA was skeptical of  
10 Abbott's ability to achieve a resistance claim at  
11 the November 27 meeting?

12 A. I think, again, the FDA was still not --  
13 hadn't seen the right body of evidence from any  
14 antibiotic application to grant resistance claims.

15 (WHEREUPON, a certain document was  
16 marked Meyer Deposition Exhibit  
17 No. 6, for identification, as of  
18 05-22-2007.)

19 BY MR. ZWICKER:

20 Q. Ms. Meyer, before you is Meyer  
21 Exhibit No. 6, which is a series of slides and a  
22 covering e-mail from Jeanne Fox to Rod Mittag and  
23 others. You are not on the e-mail.

24 Would you look at the e-mail and the

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1 enclosed slides and let me know if you recognize  
2 them.

3 A. Yes.

4 Q. How is it that you recognize them?

5 A. I was involved with working on this  
6 presentation.

7 Q. What kind of presentation was this?

8 A. Jeff Leiden was new to Abbott and he had  
9 requested kind of an overview of various projects.

10 Q. Including 773?

11 A. Yes.

12 Q. Who made the presentation to him  
13 regarding 773, do you recall?

14 A. There were a group of us.

15 Q. Were you present?

16 A. Yes.

17 Q. Do the slides that are attached to  
18 Exhibit 6 purport to summarize various issues,  
19 regulatory issues, relating to 773? Is that fair?

20 A. Yeah, they were draft.

21 Q. Who drafted them?

22 A. Jeanne Fox.

23 Q. Did you have any input on them?

24 A. I think we incorporated them into a



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1 slide doc and then made final revisions as a team.

2 Q. Take a look at -- unfortunately, every  
3 one of these pages is numbered page 1 -- the  
4 document that ends ABBT 556818.

5 A. Uh-huh.

6 Q. It's entitled "ABT-773 Regulatory  
7 Issues." Do you see that?

8 A. Yes.

9 Q. The first bullet point says,  
10 "ABT potential for QT" -- "QT prolongation." (As  
11 read.)

12 Do you see that?

13 A. Yes.

14 Q. It says, "QT is hot button for FDA"?

15 A. Yes.

16 Q. Whose term, if you know, is "hot  
17 button"? Who used that term?

18 Let me ask you a different question.

19 Would you agree with the statement that  
20 QT was a hot button issue for the FDA in  
21 November of 2000?

22 A. It was an ongoing topic in drug  
23 development for the FDA, yes.

24 Q. For anti-infectives?

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1 A. For all drugs.

2 Q. Including anti-infectives?

3 A. Yes.

4 Q. The next bullet is, "Question whether  
5 ketolides behave like macrolides." Do you see  
6 that?

7 A. Yes.

8 Q. What do you understand that to mean?

9 A. Those are two different classes. So, is  
10 there -- will FDA consider macrolide performance  
11 the same as ketolide.

12 Q. Was it your understanding that Abbott  
13 wanted to differentiate macrolides from ketolides  
14 for purposes of QT prolongation?

15 A. For purposes of all components of the  
16 drug, which would include that.

17 Q. Which would include QT prolongation?

18 A. Um-hmm.

19 Q. Would you agree that at the End of  
20 Phase II meeting in November 2000 that Abbott  
21 didn't succeed, at least at that time, in  
22 convincing the FDA that macrolides didn't behave  
23 like ketolides?

24 MS. GÜZELSU: Objection.

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1 BY THE WITNESS:

2 A. I don't remember.

3 BY MR. ZWICKER:

4 Q. We looked at an exhibit earlier, which  
5 is Exhibit No. 4, which you are free to go back to  
6 if you want. And if you would just look at the  
7 pages ending in 554.

8 A. Yes.

9 Q. Under the "Threats" section there.

10 A. Yes.

11 Q. You see it says, "Get agreement with FDA  
12 at End of Phase 2 meeting regarding EKG monitoring  
13 in Phase 3 and promote theory that QT prolongation  
14 is not class-related."

15 A. Yes.

16 Q. Fair to say that Abbott didn't succeed  
17 at the November 2000 End of Phase II meeting in  
18 convincing the FDA that there was no class  
19 relationship for QT purposes between macrolides and  
20 ketolides, correct?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. We hadn't dosed enough patients to have  
24 that answer.



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1 BY MR. ZWICKER:

2 Q. So, at that point anyway the FDA

3 wouldn't have been convinced?

4 A. It was too early.

5 Q. Look at the slide ending in 820.

6 A. Are you back to Exhibit 6?

7 Q. Oh, yeah, I am. Thank you.

8 A. Yes.

9 Q. It says, "ABT-773 potential for liver  
10 toxicity."

11 A. Yes.

12 Q. Do you see that?

13 A. Um-hmm.

14 Q. The first bullet point is, "Ketolides  
15 similar to macrolides?"

16 A. Yes.

17 Q. Do you recall the FDA expressing concern  
18 that for purposes of risk to the liver ketolides  
19 behaved like macrolides?

20 MS. GÜZELSU: Objection.

21 BY THE WITNESS:

22 A. I -- I don't recall.

23 BY MR. ZWICKER:

24 Q. Do you recall conversations within

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1 Q. And that was something that at the end  
2 of the 2000 you didn't know yet?

3 A. We had very few patients in Phase II.  
4 So, that's the purpose of Phase III.

5 MR. ZWICKER: Why don't we change the tape.

6 THE VIDEOGRAPHER: Going off the video record  
7 at 10:27 a.m.

8 (WHEREUPON, a recess was had  
9 from 10:27 to 10:31 a.m.)

10 THE VIDEOGRAPHER: And we are back on the  
11 video record at 10:31 a.m. This is Tape 2.

12 BY MR. ZWICKER:

13 Q. Ms. Meyer, if you could go back to  
14 Exhibit No. 6, and turn to page ending 821, which  
15 like every other page is entitled "ABT Regulatory  
16 Issues."

17 A. Yes.

18 Q. It says, "Indication to treat resistant  
19 pathogens." Do you see that?

20 A. Yes.

21 Q. Is that reflective of the fact that at  
22 the End of Phase II meeting Abbott indicated to the  
23 FDA that it would seek a resistance claim?

24 A. Yes.



1 Q. The next line is, "FDA skepticism  
2 regarding clinical significance of  
3 macrolide-resistant *S. pneumoniae*."

4 A. Yes.

5 Q. Do you agree with that characterization,  
6 that the FDA expressed skepticism regarding the  
7 clinical significance of macrolide-resistant  
8 *S. pneumoniae*?

9 A. Yes.

10 Q. Go back to Exhibit 4 and go back to  
11 page 554.

12 A. Yes.

13 Q. Look at the "Opportunities" section.

14 A. Yes.

15 Q. It says, going to the far right, "Get  
16 agreement" -- I read this to you before -- "with  
17 FDA at End of Phase 2 meeting regarding number of  
18 isolates required for the labeling claim."

19 Do you see that?

20 A. Yes.

21 Q. So, Abbott, it's fair to say, wasn't  
22 successful in getting the FDA to agree to the  
23 number of isolates required for labeling claim at  
24 the End of Phase II meeting, correct?

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1 A. They would not commit.

2 Q. Turn back to Exhibit 6 now, and turn to  
3 the last page ending in 822.

4 A. Yes.

5 Q. The second bullet point under  
6 "Miscellaneous" says, "Timing of IV program may  
7 affect ability to document effectiveness vs.  
8 Resistant pathogens in bacteremic patients."

9 Can you explain to me what that means?

10 A. Just in terms of based on the feedback  
11 from FDA, that they thought we should look at  
12 bacteremic patients and evaluating that to the  
13 timing of our IV program, that there was a  
14 potential impact on that.

15 Q. So that are you saying that the FDA  
16 stated that it might be necessary to have an IV  
17 program to have a resistant claim at the time that  
18 Abbott launched the adult tablet for 773?

19 MS. GÜZELSU: Objection.

20 BY THE WITNESS:

21 A. No.

22 BY MR. ZWICKER:

23 Q. What's the relationship between the  
24 timing of an IV program and the ability to achieve

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1 required back in those -- in 2000. But there is a  
2 guidance document that, you know, there's got to be  
3 a waiver requested for pediatric deferral or some  
4 type of plan for pediatric coverage.

5 Q. And if there isn't?

6 A. I think that's part of the whole  
7 regulatory negotiation. Again, I'm not a  
8 regulatory expert.

9 Q. Do you have the understanding that  
10 unless you satisfy the pediatric rule that you  
11 can't obtain approval of an adult tablet with the  
12 FDA?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. I don't think there is anything that  
16 requires that for the original approval, but there  
17 will be ongoing discussions with the FDA at the  
18 approval time frame of what the pediatric plan  
19 looks like.

20 (WHEREUPON, a certain document was

21 marked Meyer Deposition Exhibit

22 No. 7, for identification, as of

23 05-22-2007.)

24 MR. ZWICKER: Before the witness is a document



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1 titled "ABT-773 Portfolio Review" dated December 5,  
2 2000, and it bears Bates Nos. ABBT 577000 through  
3 168.

4 BY MR. ZWICKER:

5 Q. Ms. Meyer, would you just briefly review  
6 the document and tell me if you recognize it.

7 A. Yes.

8 Q. Is this the document that was prepared  
9 in connection with the presentation to  
10 Dr. Leiden --

11 A. Yes.

12 Q. -- that you testified to earlier?

13 A. Yes.

14 Q. What was your role in the presentation?  
15 On what matters did you present on, if any?

16 A. The IV program, the pediatric and the  
17 Japan program.

18 Q. Why did you present on the IV program?

19 A. Because Carl asked me to.

20 Q. How did you prepare to present on the IV  
21 program?

22 A. We discussed the key issues we wanted to  
23 bring up and we created slides. I drafted them and  
24 as part of the whole team we evaluated the whole



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1 A. Based on this document, it says  
2 August '03.

3 Q. You have no reason to doubt that's  
4 accurate, correct?

5 A. That was our plan at the time we made  
6 the presentation.

7 Q. Okay.

8 (WHEREUPON, a certain document was  
9 marked Meyer Deposition Exhibit  
10 No. 8, for identification, as of  
11 05-22-2007.)

12 MR. ZWICKER: Before the witness is Meyer  
13 Exhibit No. 8, which is a project report for  
14 ABT-773 for February 2001, and it has Bates Nos.  
15 387 through 399.

16 BY MR. ZWICKER:

17 Q. Ms. Meyer, do you recognize the format  
18 of these -- of this document?

19 A. Yes, I do.

20 Q. Is this the kind of document that you  
21 would draft?

22 A. Yes.

23 Q. Take a look at page 387.

24 A. This front page?

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1 Q. Is that consistent with your  
2 recollection?

3 A. Yes.

4 Q. At the December '01 meeting with  
5 Dr. Leiden --

6 MS. GÜZELSU: I'm sorry. December '01?

7 BY THE WITNESS:

8 A. December 2000.

9 BY MR. ZWICKER:

10 Q. December 2000. Thank you.

11 Do you recall any issues regarding

12 funding for the IV program?

13 A. We hadn't funded some of the activities,  
14 correct.

15 Q. And, in fact, isn't it true that the IV  
16 program was unfunded for 2001?

17 MS. GÜZELSU: Objection.

18 BY MR. ZWICKER:

19 Q. Let me point you to a document if that  
20 helps you out.

21 A. I think it's 147.

22 Q. Yeah, take a look at 147.

23 A. Yes. It looks like for based on that  
24 point in time that they did not have approved

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1 funding for the IV.

2 Q. For 2001?

3 A. Correct.

4 Q. And the -- as of December of 2000, the  
5 2001 funding decisions would have already been  
6 made, correct?

7 A. The initial, yes.

8 Q. Based on the document that bears Bates  
9 No. 147, is it fair to say that for 2001 Abbott  
10 required \$7 million to fund development of an IV  
11 formulation?

12 MS. GÜZELSU: Objection.

13 BY THE WITNESS:

14 A. I think that based on the activities  
15 that were planned in 2001 there was a \$7 million  
16 cost of all activities.

17 BY MR. ZWICKER:

18 Q. For 2001?

19 A. Correct, based on these milestones.

20 Q. The last bullet on page 147 says,  
21 "IV will help to obtain resistant S. pneumoniae  
22 claim."

23 A. Yes.

24 Q. Do you see that?

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1 A. Yes.

2 Q. Can you explain to me why that's so?

3 A. Again, the severe CAP patients would be  
4 treated in hospital most likely with an IV. So, it  
5 would be an added benefit to have the IV.

6 Q. And you wrote this slide, correct?

7 A. I would have helped -- yeah, I'm not  
8 sure exactly if I wrote it or if I drafted it and  
9 we edited together.

10 Q. So, you would agree with the statement  
11 that IV would help Abbott?

12 A. It would be an asset. It would be an  
13 additional asset.

14 Q. To helping Abbott achieve a resistance  
15 claim?

16 A. Yes.

17 (WHEREUPON, a certain document was  
18 marked Meyer Deposition Exhibit  
19 No. 9, for identification, as of  
20 05-22-2007.)

21 MR. ZWICKER: Before the witness is Meyer  
22 Exhibit No. 9, which is a document titled "ABT-773  
23 Update February 12, 2001," bearing Bates Nos.  
24 ABBT 205042 through 205046.



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1 BY MR. ZWICKER:

2 Q. Ms. Meyer, would you review this  
3 document and let me know when you're done.

4 A. Okay.

5 Q. Do you recognize this document?

6 A. Yes.

7 Q. Did you write it?

8 A. I would have drafted it with the input  
9 of team members, yes.

10 Q. Looking at the section marked "Key  
11 issues facing the ABT-773 development program" --

12 A. Yes.

13 Q. -- "are summarized below."

14 A. Yes.

15 Q. What team members would have helped you  
16 draft the sections relating to QTc and liver  
17 toxicity?

18 A. Let's see. February of 2001. It would  
19 have been Joaquin Valdes, Carl Craft, George  
20 Aynilian.

21 Q. And when you drafted this document, did  
22 you submit it to other team members for their  
23 comments?

24 A. I would have submitted it most likely to

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1 Joaquin and Carl.

2 Q. For comments?

3 A. For comments.

4 Q. And if they had given you any, would you

5 have incorporated them?

6 A. Of course.

7 Q. And what did you do with this document

8 when you completed it? Who did you give it to?

9 A. I don't remember.

10 Q. When you completed this document and

11 incorporated all the comments that you received,

12 did you feel that it accurately and completely

13 reflected the views of the development team

14 regarding the status of 773 on February 12, 2001?

15 MS. GÜZELSU: Objection.

16 BY THE WITNESS:

17 A. Yes.

18 BY MR. ZWICKER:

19 Q. Let's focus on "QTc Issues," which

20 begins on page 042.

21 A. Okay.

22 Q. And runs over to 043.

23 A. Yes.

24 Q. The first full paragraph on 043 --

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1 A. Um-hmm.

2 Q. -- begins with the following sentence:

3 "The ketolide ABT-773 will be considered guilty  
4 until proven innocent because it is related to  
5 erythromycin and clarithromycin which are also  
6 suspect and under scrutiny."

7 Do you see that?

8 A. Yes.

9 Q. Tell me why you used that language.

10 MS. GÜZELSU: Objection.

11 BY THE WITNESS:

12 A. I don't recall.

13 BY MR. ZWICKER:

14 Q. Is it fair to say that you believe that  
15 the FDA, based on your participation in meetings,  
16 presumed that 773 posed risks to the heart until  
17 Abbott convinced it otherwise?

18 MS. GÜZELSU: Objection.

19 BY THE WITNESS:

20 A. All drugs would be presumed that way.

21 BY MR. ZWICKER:

22 Q. Presumed guilty until proven innocent  
23 you mean?

24 A. Absolutely.



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1 Q. Fair to say in your own mind, having  
2 used this language, that you considered the FDA's  
3 scrutiny of QTc issues to be pretty rigorous,  
4 correct?

5 A. It was a growing hurdle.

6 Q. Look at the section marked "Liver  
7 Toxicity."

8 A. Yes.

9 Q. It says, "The FDA has similar concerns  
10 regarding the potential for liver toxicity of new  
11 drugs as it has for QTc issues, since both of these  
12 problems have resulted in drugs being removed from  
13 the market shortly after approval."

14 Do you see that?

15 A. Yes.

16 Q. Would you agree based on your use of the  
17 word that the FDA has similar concerns that the FDA  
18 also, when it came to the impact of 773 on the  
19 liver, considered it guilty until proven innocent?

20 MS. GÜZELSU: Objection.

21 BY THE WITNESS:

22 A. I don't remember that assumption. It's  
23 metabolized by the liver. So, there would be  
24 definite concern about liver toxicity.



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1 BY MR. ZWICKER:

2 Q. So, would you agree based on your  
3 experience with the FDA that the FDA was rigorously  
4 scrutinizing the impact of 773 on the liver?

5 A. As it would for all antibiotics, yes.

6 Q. Turn the page to page 044. There is a  
7 paragraph beginning "In the Japanese study run in  
8 Hawaii."

9 A. Yes.

10 Q. It says, "We saw increases in LFTs in  
11 Japanese subjects."

12 A. Correct.

13 Q. "This was very disturbing, since LFTs  
14 were seen only in the Japanese subjects."

15 What is LFT?

16 A. Liver function tests.

17 Q. Do you recall discussions with anyone on  
18 the 773 team regarding the impact of the Japanese  
19 study on risks to the liver posed by 773?

20 A. It didn't -- you know, we got results we  
21 didn't expect.

22 Q. Didn't expect in what respect?

23 A. Due to -- after analyzing how this study  
24 was run, we recognized that they had put Japanese

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1 subjects on the wrong diet and there were other  
2 problems with the patients they included in the  
3 trial. So, we saw liver enzyme elevations we  
4 didn't expect.

5 Q. Were you concerned that the elevated  
6 liver function tests were a function of the drug or  
7 a function of the diet that people were taking or a  
8 mixture of both?

9 A. We didn't know it until we did the  
10 evaluation, but we determined it was based on the  
11 high die -- high caloric diet that we put the  
12 subjects on.

13 Q. And not on the drug?

14 A. Correct.

15 Q. Turn -- at the very bottom of the  
16 page it says, "ABT-773 IV Formulation" --

17 A. Yes.

18 Q. -- "Program."

19 A. Um-hmm.

20 Q. Turn the page. It says, "The IV  
21 formulation program is presently unfunded. The IV  
22 program is important to overall" funding -- "to  
23 overall program because of the following."

24 Do you see that?

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1 A. Yes.

2 Q. So, is it consistent with your

3 recollection that as of February 12, 2001, that the

4 IV program was still unfunded?

5 A. I don't recall if we had gotten some

6 funding because we had proposed milestone funding

7 it.

8 This product is marketed between PPD and

9 HPD. So, it has very small impact on the overall

10 market share for the product.

11 Q. Are the only funding sources for the IV

12 formulation PPD and HPD?

13 A. Potentially AI could also have provided

14 some funding.

15 Q. But just those three?

16 A. Yes.

17 Q. But just to go back to my question, you

18 have no reason to doubt the accuracy of your

19 statement here that as of February 12, 2001, that

20 the IV program was unfunded?

21 A. The entire program was unfunded. I

22 don't recall if it had been milestone funded at

23 that time.

24 Q. What do you mean by milestone funded?



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1 A. To get the information on the first  
2 study, to fund the first study to get that first  
3 decision and to know if we had something that we  
4 could move forward with further development.

5 Q. Look at the next paragraph where it  
6 says, "The ABT-773 IV program received partial  
7 funding last year from both PPD and HPD" --

8 A. Correct.

9 Q. -- "but has not been funded for 2001."

10 A. Um-hmm.

11 Q. Does that refresh your recollection  
12 about whether it had been --

13 A. It looks like at that point it had not  
14 yet been funded for 2001.

15 Q. Under "2001 funding." Do you see that?

16 A. Yes.

17 Q. Under 045. It says, "HPD first pass  
18 funding cut for 773 IV (7 million)."

19 Do you see that?

20 A. Yes.

21 Q. What does that mean?

22 A. That means that they proposed the  
23 7 million in the first pass budget review and it  
24 was cut from the first review.



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1 know, you have to allocate funds appropriately  
2 based on activities ongoing.

3 Q. And if the IV program hadn't been  
4 funded, the risk would have been that it would have  
5 delayed the filing of the IV formulation?

6 A. Potentially.

7 Q. And the risk of a delayed filing would  
8 be that it might impact the ability of Abbott to  
9 achieve a resistance claim for 773?

10 A. There was some possibility, but at the  
11 time we were attempting to achieve the claim with  
12 the tablet formulation.

13 Q. Take a look at -- back on Exhibit 9  
14 here, where it says "Pediatric Program."

15 A. Yes.

16 Q. Do you see that?

17 A. Uh-huh.

18 Q. You prepared slides for the pediatric  
19 program?

20 A. Yes.

21 Q. Correct?

22 A. Right.

23 Q. It says on the very last page, page 046,  
24 that the pediatric suspension program is on hold.

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1 Do you see that?

2 A. That's correct.

3 Q. Why was that?

4 A. Because the compound is five to seven

5 times more bitter than clarithromycin.

6 Q. So, there were issues relating to taste

7 that needed to be resolved?

8 A. Yes, significant issues.

9 Q. Reading further down the page it

10 says, "Even with the difficulties of making an

11 acceptable formulation, the pediatric formulation

12 would have benefits including increasing the

13 perception of safety, better pricing, and

14 acceptance in European markets and FDA requires

15 studies in pediatrics."

16 Do you see that?

17 A. Yes.

18 Q. Does this help refresh your recollection

19 of what the nature of the FDA's requirements were

20 regarding pediatric studies?

21 A. Yes. However, again, depending on the

22 drug itself, you would either file a waiver to

23 defer them or to not do them at all based on

24 properties of the drug.

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1 Q. Did you personally believe that it was  
2 important to have pediatric studies ongoing at the  
3 time Abbott applied for approval to the FDA for  
4 773?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. I don't recall that they had to be  
8 ongoing at the time you applied for the adult  
9 indication.

10 BY MR. ZWICKER:

11 Q. You don't recall one way or another?

12 A. I don't recall the timing of when they  
13 should have been going on when the adult  
14 formulation was filed.

15 Q. Okay.

16 (WHEREUPON, a certain document was  
17 marked Meyer Deposition Exhibit  
18 No. 10, for identification, as of  
19 05-22-2007.)

20 MR. ZWICKER: Before the witness is Meyer  
21 Exhibit No. 10, which is a document entitled  
22 "ABT-773 Update, February 12, 2001."

23 BY MR. ZWICKER:

24 Q. Ms. Meyer, could you look at this



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1 document and see if you recognize it.

2 Just for the record it's dated the same

3 day as Exhibit No. 9, which is the 773 update.

4 A. Yes. I recognize it.

5 Q. What is it?

6 A. It's a presentation that we gave to the

7 Pharmaceutical Executive Committee.

8 Q. On February 12, 2001 or thereabouts?

9 A. Thereabouts.

10 Q. What was the nature of the presentation

11 to the PEC?

12 A. It was the first formal Pharmaceutical

13 Executive Committee meeting and, again, it was an

14 overview of programs.

15 Q. And this is -- there had been a meeting

16 in December, correct?

17 A. Only with Jeff Leiden, not with the

18 Pharmaceutical Executive Committee.

19 Q. The February meeting was for all

20 compounds under development, is that right?

21 A. I don't recall the agenda, but I

22 remember there were a number of compounds

23 presented.

24 Q. Did you present with respect to 773?



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1 A. No, I did not.

2 Q. Did you attend the PEC meeting on

3 February 12?

4 A. Yes, I did.

5 Q. Who -- was Dr. Leiden present at that

6 one as well?

7 A. Yes, he was.

8 Q. And Dr. Leonard?

9 A. Yes, Dr. Leonard was there.

10 Q. Who presented for 773 at the February 12

11 meeting?

12 A. Dr. Carl Craft.

13 Q. Carl Craft is no longer at Abbott?

14 A. That's correct.

15 Q. He left while you were still an

16 employee?

17 A. Yes, he did.

18 Q. Where did he go, do you know?

19 A. He went to Medicines For Malaria Venture

20 in Switzerland.

21 Q. If you wouldn't mind, turn to page 6855,

22 which begins with "ABT-773 IV Program."

23 A. Okay.

24 Q. Did you prepare the slides for the IV

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1 Q. Do you know --

2 A. So, delaying it would have impact.

3 Sorry.

4 Q. Do you actually know the amount of  
5 decreased value resulting from a delay of more than  
6 one year for an IV formulation?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. No, I do not.

10 BY MR. ZWICKER:

11 Q. So, in fact, it could be a loss of value  
12 that's in excess of just the 36 million for  
13 stepdown therapy, correct?

14 A. Hard to estimate.

15 One thing I would add is that we did  
16 have verbal approval from Jeff Leiden to move  
17 forward with the IV single rising dose study in  
18 December when he was there because we, you know,  
19 it's a small amount of money compared to the  
20 overall cost of the development. So, he gave us  
21 verbal approval to move forward with the activity.

22 I don't think it's reflected in any  
23 slides, but we had started some of the plans to get  
24 the Phase I study started based on his verbal

1 agreement.

2 Q. Let's go back to Exhibit No. 9.

3 A. Yes.

4 Q. And there is on page 045, there is a

5 series of milestones for the IV --

6 A. Yes.

7 Q. -- program?

8 A. Um-hmm.

9 Q. Can you find for me on Exhibit No. 9 the

10 portion of the IV program that was approved by

11 Dr. Leiden in December of 2000?

12 A. Yes, it was the single dose rising

13 Phase I study.

14 Q. Is that -- is it listed -- is it written

15 as "Milestone funding to Phase I Go/No Go

16 (1 million)," is that the one you're talking about?

17 A. Well, I'm referring to the first bullet

18 point where it says "Single rising dose Phase I

19 study" and --

20 Q. I see.

21 A. -- it may be also including -- the

22 million dollars probably included both single

23 rising dose and multiple dose. So I think the

24 single rising dose study was probably a half a

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1 million dollars.

2 Q. But, nonetheless, the funding that you  
3 believed was necessary for 2001 for the IV program  
4 was \$7 million, correct?

5 A. 7 million was to get you to start of  
6 Phase III.

7 Q. Which Abbott or at least you hoped to do  
8 by the end of 2001?

9 A. December of 2001 we would want to  
10 initiate some of the studies. So, there would be  
11 start-up costs for Phase III plus the Phase I  
12 program.

13 Q. And \$7 million was required in 2001  
14 to --

15 A. Start up Phase III.

16 Q. To start up Phase III?

17 A. Yes.

18 (WHEREUPON, a certain document was  
19 marked Meyer Deposition Exhibit  
20 No. 11, for identification, as of  
21 05-22-2007.)

22 MR. ZWICKER: Before the witness is  
23 Exhibit No. 11 which is an e-mail and covering  
24 "ABT-773 Development Plan" that bears Bates Nos.



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1 204959 through 205041.

2 BY THE WITNESS:

3 A. Yes.

4 BY MR. ZWICKER:

5 Q. Ms. Meyer, is that the document that

6 when you referred to a development plan before that

7 you drafted?

8 A. It looks like a draft or a -- some type

9 of -- notice the bookmarks are not defined. So

10 there must be -- I don't know if this is the final

11 version, but it's certainly a development plan

12 document, yes.

13 Q. That you would have worked on?

14 A. Yes, um-hmm.

15 Q. The cover page, the e-mail on the front

16 of that document, reflects a communication from

17 Eugene Sun to Dr. Bukofzer. Do you see that?

18 A. Yes.

19 Q. Do you recall when Dr. Bukofzer joined

20 the venture?

21 A. It would have been March of 2001.

22 Q. Do you know why he joined the venture?

23 A. He replaced Carl Craft.

24 Q. Because Carl Craft had left?

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1 A. He was -- yes, he left in March.

2 Q. Did you participate in providing

3 Dr. Bukofzer with information to -- so that he

4 could understand the issues facing 773?

5 A. Yes.

6 Q. What information did you provide him?

7 A. Background information on the project,

8 history, status.

9 Q. Did you have conversations with him

10 regarding the status of 773 as of March 2001?

11 A. Yes.

12 Q. Do you recall any conversations with him

13 regarding the FDA's scrutiny of QT and liver issues

14 on 773?

15 A. We would have gone over status of all

16 the functions. So, regulatory would have been

17 included.

18 Q. Do you remember whether he shared your

19 view that 773 was presumed guilty until declared

20 innocent regarding liver and heart issues?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. I don't -- I don't recall using those

24 words, and certainly it's the same issue on any

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1 drugs under development. So, it would be part of a  
2 normal process.

3 BY MR. ZWICKER:

4 Q. Do you recall whether he shared your  
5 concern that the FDA was closely scrutinizing heart  
6 and liver issues?

7 MS. GÜZELSU: Objection.

8 BY THE WITNESS:

9 A. We had EKG monitoring in the studies  
10 that we were just initiating. So, we had -- we  
11 were proceeding with all the necessary and expected  
12 monitoring for the studies for those issues.

13 BY MR. ZWICKER:

14 Q. And you brought him up to speed on that?

15 A. He would have looked at the study  
16 protocols, part of the, you know, feedback from End  
17 of Phase II and seen that.

18 Q. Did he express any concern to you about  
19 whether the FDA's scrutiny of 773 from the  
20 standpoint of liver and heart was extremely  
21 challenging or insurmountable?

22 A. No.

23 Q. Do you remember him expressing any views  
24 to you regarding the fact that once-a-day dosing



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1 was not achievable when he took over?

2 A. We were in Phase III at that time, so

3 that question was still to be answered.

4 Q. It was still to be answered as of

5 March 2001?

6 A. Absolutely.

7 Q. Do you express -- do you recall or have

8 any recollection of him discussing with you the

9 implications of a once-a-day as opposed to a

10 twice-a-day dosing decision?

11 A. Not in March.

12 Q. Later?

13 A. It would have been as we got more data.

14 (WHEREUPON, a certain document was

15 marked Meyer Deposition Exhibit

16 No. 12, for identification, as of

17 05-22-2007.)

18 MR. ZWICKER: Before the witness is

19 Exhibit No. 12, which is an e-mail from -- two

20 e-mails and they bear Bates No. ABBT 568172.

21 BY MR. ZWICKER:

22 Q. Ms. Meyer, if you don't mind reviewing

23 this, and I appreciate that you're not a recipient

24 of it.



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1    perversion issues this would be a not most likely a  
2    viable scenario for this drug.

3       Q.   And by saying that you mean that it was  
4    going to be difficult to formulate a pediatric  
5    version of the drug?

6       A.   Yes, that would be acceptable.

7       Q.   That would be acceptable?

8       A.   To patients.

9       Q.   And were the difficulties that Abbott  
10   was encountering with a drug that would be  
11   acceptable to a patient population, was that a  
12   reason why the project wasn't funded according to  
13   this e-mail?

14       MS. GÜZELSU: Objection.

15       BY MR. ZWICKER:

16       Q.   Let me ask you a different question.  
17   That's a bad question.

18       Do you know why -- the e-mail says that  
19   the pediatric project isn't funded. The e-mail is  
20   dated February 14, 2001.

21       A.   Yes.

22       Q.   Do you know as of February 14, 2001  
23   whether the pediatric program was funded?

24       A.   Yeah, it was based on the taste

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1 assessments we had done on the prototypes. I don't  
2 remember the date. But we had already done a lot  
3 of formulation work and had not identified an  
4 appropriate formulation.

5 Q. So, as of that point, February 14, 2001,  
6 the pediatric program was not funded?

7 A. There was --

8 MS. GÜZELSU: Objection.

9 BY THE WITNESS:

10 A. -- no formulation available to do  
11 phase -- you know, continued development at that  
12 point.

13 BY MR. ZWICKER:

14 Q. So, then, no dollars were committed for  
15 future development at that point?

16 A. At that point, yes.

17 (WHEREUPON, a certain document was  
18 marked Meyer Deposition Exhibit  
19 No. 13, for identification, as of  
20 05-22-2007.)

21 MR. ZWICKER: Before the witness is  
22 Exhibit No. 13, which is a document titled "Abbott  
23 Portfolio Review, March 7 to 9, 2001," and it bears  
24 Bates Nos. 13203 through 13214, and I'll note for

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1 A. There wasn't enough data yet to make a  
2 final conclusion.

3 Q. For 773?

4 A. That's correct. We were in the --  
5 within Phase III.

6 (WHEREUPON, a certain document was  
7 marked Meyer Deposition Exhibit  
8 No. 15, for identification, as of  
9 05-22-2007.)

10 (WHEREUPON, discussion was had off  
11 the record.)

12 MR. ZWICKER: Before the witness is  
13 Exhibit No. 15, which is a descriptive memorandum  
14 for ABT-773 titled -- dated February 2001 and  
15 bearing Bates Nos. 8153 through 8158.

16 BY MR. ZWICKER:

17 Q. Ms. Meyer, take a look at this document  
18 and tell me if you recognize it.

19 A. The content is familiar, but I don't  
20 recognize this format or this, you know, the title  
21 of this document.

22 Q. When you say "the content is familiar,"  
23 what do you mean?

24 A. Very similar content to what we've seen



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1 in other presentations in the development plan.

2 Q. Do you ever recall being asked by

3 Dr. Leonard to prepare a status report for 773 in

4 connection with an investment made by John Hancock?

5 A. No, I do not.

6 Q. Did you -- putting aside your

7 conversations with counsel, were you aware in 2001

8 that John Hancock was investing in 773?

9 A. I was aware that there were a group of

10 compounds that were under an agreement with John

11 Hancock, but I don't remember the dates of when

12 that was communicated to the employees.

13 Q. Do you remember who communicated that

14 fact to you?

15 A. It would have been an all-employee

16 communication, so it would have come through public

17 relations.

18 Q. Do you recall being called upon to

19 provide any information regarding 773 in connection

20 with the John Hancock investment?

21 A. No, I -- I don't recall.

22 Q. Do you know anyone who was called upon

23 to provide information regarding 773 on your team?

24 A. I don't remember there being anybody



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1 specifically.

2 Q. Take a look at page 2 where it says

3 "ABT-773, Opportunity Overview."

4 A. Yes.

5 Q. The second paragraph --

6 A. Yes.

7 Q. -- says, "Product features such as high

8 efficacy, activity against resistant strains of

9 bacteria and convenience should enable it to

10 compete against both Zithromax and newer agents

11 such as the quinolones. Dosing is expected to be

12 once-a-day."

13 Do you see that?

14 A. Yes.

15 Q. I'm going to ask you some questions as

16 of March 13, 2001.

17 A. Okay.

18 Q. This document is dated as of February.

19 A. Yes.

20 Q. It's fair to say, isn't it, that as of

21 March 13, 2001, Abbott hadn't yet determined

22 whether dosing for 773 would be once a day or twice

23 a day, correct?

24 A. We were in Phase III. So we wouldn't

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1 have had the data to make those decisions yet.

2 Q. Turn to page 4. "Scientific Rationale

3 for 773."

4 A. Yes.

5 Q. Look at the second line. It says, "Good

6 activity against resistant Gram."

7 What does "Gram" mean?

8 A. Gram positive, that's based on -- gram

9 negative and gram positive is how you classify

10 organisms. If you look under a microscope, they --

11 they differentiate into gram negative, gram

12 positive.

13 Q. Okay. It says, "Good activity against

14 resistant Gram plus organisms, particularly

15 macrolide-resistant *S. pneumoniae*."

16 Do you see that?

17 A. That's correct.

18 Q. Fair to say that based on your meetings

19 with the FDA, the FDA wasn't convinced that as a

20 clinical matter there was such a thing as

21 macrolide-resistant *S. Pneumoniae*. True?

22 A. This is definitely looking at the

23 profile in vitro. So, we had proven good activity

24 in vitro. So, again, you are looking for how in

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1 vitro is replicated in a clinical population which  
2 you only get during Phase III trials, which we were  
3 in the middle of doing.

4 Q. And how 773 did in those Phase III  
5 clinical trials would have an impact on whether or  
6 not there could be a credible resistance claim for  
7 macrolide-resistant pneumonia, correct?

8 A. Based on clinical --

9 MS. GÜZELSU: Objection.

10 THE WITNESS: Sorry.

11 BY MR. ZWICKER:

12 Q. You can answer.

13 A. I'm sorry.

14 Yeah, based on clinical evidence.

15 Q. So, it's fair to say that Abbott would  
16 be uncertain whether or not as a clinical matter it  
17 would be able to achieve activity against  
18 macrolide-resistant *S. pneumoniae*. True?

19 A. Until the data was finished, yes.

20 Q. The last line says, "Oral Suspension and  
21 I.V. forms enabling penetration into pediatrics and  
22 hospital segments"?

23 A. Yes.

24 Q. As of March 13, the IV program was still



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1 unfunded for 2001, correct?

2 MS. GÜZELSU: Objection.

3 BY THE WITNESS:

4 A. Again, we had started preparation for  
5 the first Phase I based on verbal agreement with  
6 Jeff Leiden to, you know, start that process, but  
7 we were still waiting funding decisions on the rest  
8 of the program.

9 BY MR. ZWICKER:

10 Q. And you couldn't be sure whether you  
11 would get funding for the rest of the program or  
12 not?

13 MS. GÜZELSU: Objection.

14 BY THE WITNESS:

15 A. Well, we wanted to start the Phase I  
16 study so we'd answer some questions.

17 BY MR. ZWICKER:

18 Q. But in terms of whether you'd have the  
19 funding sufficient to complete the program, you  
20 couldn't tell that yet, correct?

21 MS. GÜZELSU: Objection.

22 BY THE WITNESS:

23 A. But that's the nature of all drug  
24 development projects, you're always in a funding



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1 cycle.

2 BY MR. ZWICKER:

3 Q. But the answer is you still can't -- you

4 don't know at that point?

5 MS. GÜZELSU: Objection.

6 BY THE WITNESS:

7 A. None of -- I mean that's typical for any

8 program.

9 BY MR. ZWICKER:

10 Q. And just reading on, it says, "Oral

11 Suspension and I.V. forms enabling penetration into

12 pediatric and hospital segments."

13 The document we just saw showed that as

14 of February 12, 2001, the pediatric program was on

15 hold, correct?

16 A. We had finished some formulation work

17 and hadn't found a satisfactory formulation, so we

18 didn't have additional studies planned that were

19 funded, correct.

20 Q. Were -- were you familiar in connection

21 with your job in the -- in the venture about

22 regulatory scrutiny of 492?

23 A. It would have been similar as it was

24 another antibiotic. So, it would have similar



Errata Sheet

Page: 1 Of Total Pages: 2

I wish to make the following changes to my deposition/statement:

Page #: 13, Line #: 17

As appears in Transcript: time meetings

To: team meetings

Reason: typo

Page #: 79, Line #: 13

As appears in Transcript: regulatory

To: regularly

Reason: typo

Page #: 116, Line #: 10

As appears in Transcript: NEC

To: NCE

Reason: typo

Page #: 122, Line #: 11

As appears in Transcript: Humira

To: Humira

Reason: typo

6/26/07  
DATE

Carol S. Meyer  
DEPONENT'S SIGNATURE

Errata Sheet

Page: 2 Of Total Pages: 2

I wish to make the following changes to my deposition/statement:

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Reason: typo

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6/26/07  
DATE

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CAROL SUSAN MEYER, MAY 22, 2007

203084

1 UNITED STATES DISTRICT COURT  
2 FOR THE DISTRICT OF MASSACHUSETTS  
3

4 JOHN HANCOCK LIFE INSURANCE )

5 COMPANY, et al., )

6 Plaintiffs, )

7 -vs- )

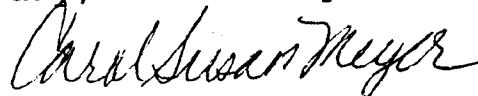
Civil Action No.

8 ABBOTT LABORATORIES, )

05-11150-DPW

9 Defendant. )

10  
11 I hereby certify that I have read the  
12 foregoing transcript of my deposition given at the  
13 time and place aforesaid, consisting of Pages 1 to  
14 191 inclusive, and I do again subscribe and make  
15 oath that the same is a true, correct and complete  
16 transcript of my deposition so given as aforesaid,  
17 and includes changes, if any, so made by me.

18 

19 CAROL SUSAN MEYER

20 SUBSCRIBED AND SWORN TO

21 before me this day

22 of , A.D. 200\_\_.

23 Notary Public  
24



1

# **Deposition Exhibit 1**

**P's Exhibit HV**



Tim  
Vanbiesen/LAKE/PPRD/  
ABBOTT

03/16/2000 09:18 AM

To Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject Abt. 773 Dosing Strategy Kick-off Meeting

Forwarded by Tim Vanbiesen/LAKE/PPRD/ABBOTT on 03/16/2000 09:18 AM

Keith F Hendricks  
01/26/2000 04:55 PM

To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT,  
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K Flamm/LAKE/PPRD/ABBOTT@ABBOTT, Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Linda E  
Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Charles Locke/LAKE/PPRD/ABBOTT@ABBOTT, Gregory  
Bosco/LAKE/PPRD/ABBOTT@ABBOTT, George Aynlian/LAKE/PPRD/ABBOTT@ABBOTT, Laura  
Robinson/LAKE/AI/ABBOTT@ABBOTT, Jean-Paul Kress/LAKE/AI/ABBOTT@ABBOTT, Nigel  
Livesey/LAKE/AI/ABBOTT@ABBOTT, Jessie R Groothuis/LAKE/AI/ABBOTT@ABBOTT, Bonnie J  
Shaul/LAKE/AI/ABBOTT@ABBOTT  
cc: Steve C Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, Steve Cohen/LAKE/PPRD/ABBOTT@ABBOTT,  
Tim Vanbiesen/LAKE/PPRD/ABBOTT@ABBOTT, mchang@sdg.com, Tony C  
Deahl/LAKE/AI/ABBOTT@ABBOTT  
Subject: Abt. 773 Dosing Strategy Kick-off Meeting

Greetings,

We now need to turn our attention to the very important task of formulating the dosing strategy for Abt 773. Mark Chang, of SDG, will be facilitating the decision-making process along with 2-3 other Abbott personnel. The likely core team for this assessment is shown below, but this can be discussed and finalized at the kick-off meeting. The kick-off meeting will be from 1-5 on Monday, January 31st. The location has not yet been determined.

As we discussed in our last meeting, the timeline for completing this assessment will be tight, so it will most certainly require calendar prioritization from all of us. But as we also discussed, there is no more important issue for us to make a decision on right now in our entire portfolio, so the time will be well spent. However, Mark will try to organize the activities to make the most efficient use of our valuable time as possible.

Given the time constraints, it is especially important for as many of you as possible to be at the kick-off meeting. I look forward to seeing you there.

Regards,

Keith Hendricks

PPD Team Members :

David D Morris

Carl Craft

Rosemarie K Waleska

Richard G Granneman

Susan J Semla

Confidential



ABBT305783

Robert K Flamm  
Rod M Mittag  
Linda E Gustavson  
Charles Locke  
Greg Bosco  
George Aynilian

AI Team Members :  
Keith Hendricks  
Nigel Livesey  
Laura Robinson  
Jean-Paul Kress  
Jessie Groothuis  
Bonnie Shaul



## **Deposition Exhibit 3**

**P's Exhibit HW**



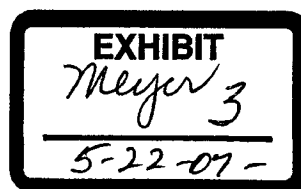
**ABT-773**  
**KETOLIDE ANTIBIOTIC**

**2000 Strategic Marketing Plan**  
**June 2000**

**Rod Mittag**  
**Manager, New Product Development**

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*ABT-773 Strategic Marketing Plan*



CONFIDENTIAL  
ABBT0570747

*The objective of this strategic document is to develop a common foundation for the commercial development of ABT-773. This plan includes the strategy for execution of the strategic marketing plan.*

*This document presents the domestic marketing plan for ABT-773. An ex-U.S. marketing plan will be developed by Abbott International New Product Planning.*

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## I. EXECUTIVE SUMMARY (NOT REVISED)

ABT-773 is a ketolide antibiotic currently under development by PPD. A tableted formulation is currently being evaluated in Phase II clinical studies. Indications are being sought for acute bacterial exacerbations of chronic bronchitis (ABECB), community-acquired pneumonia (CAP), and acute maxillary sinusitis (AMS).

It is anticipated that ABT-773 will file with the FDA in December 2001 and be approved December 2002.

I.V. and oral suspension (pediatric) formulation development has not yet been funded, though funding is anticipated for FY2000. Development plans for these formulations are being established.

Total U.S. antibiotic sales in 1998 were \$7.7 billion, comprised of \$4.8 billion in tab/cap sales, \$1.9 billion in pediatric sales, and \$1.0 billion in I.V. sales. While the use of antibiotics has been decreasing (TRX CAGR<sub>95-98</sub> of -3.5%), sales of antibiotics has been increasing (Sales CAGR<sub>95-98</sub> of +3.4%). Key market drivers are:

- Resistance to antibiotics will continue to increase. Physicians will be urged to restrict the use of antibiotics for documented, severe infections and to choose agents with an appropriate spectrum of activity relative to the infection being treated.
- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant competitive threat. Up to five new quinolones will reach the market prior to ABT-773.
- Convenience attributes such as QD dosing and short course of therapy (5-7 days) will become commonplace and will offer little in the way of differentiation; adverse events and drug-drug interactions will continue to be important attributes.
- Unmet need in the antibiotic market is very low. Companies will turn to new efficacy metrics as a means of differentiating their products. Efficacy toward resistant organisms will be an important new metric. PK/PD parameters will also be exploited to gain competitive advantage.
- Several key branded antibiotics will lose patent exclusivity over the next three to five years, resulting in increasing price sensitivity within the antibiotic market. This will create opportunity in the pediatric market, however, as the top three pediatric brands are among those losing patent exclusivity.
- Two antiviral influenza agents will reach the market in 1999, with others likely in the future. Given that a considerable amount of antibiotic business stems from inappropriate use for influenza, the companies launching these agents will likely exploit the increasing of awareness of appropriate use and encourage physicians forgo the use of antibiotics in lieu of the new antiviral agents. Increasing use of currently available point-of-care diagnostic kits will allow physicians to distinguish bacterial infection from influenza.

The success of ABT-773 will depend on the extent to which it can differentiate itself from this competitive field.



## II. INTRODUCTION

Ketolides are a relatively new class of antibiotics that are based on a macrolide-like structure. The ketolide ABT-773 is being evaluated in the treatment of acute exacerbations of chronic bronchitis (AECB), tonsillitis/pharyngitis, community-acquired pneumonia (CAP), and acute bacterial sinusitis.

A Phase IIa bronchitis study was completed in June 1999. Based on this study and on phase I PK and formulation studies, a "Go" decision was made to continue development. Phase IIb dose-ranging studies were initiated in September 1999 with 150 mg, 300 mg, and 600 mg QD formulation for in AECB (5 days), CAP (7 days), and sinusitis (10 days; 150 mg was not evaluated in sinusitis). Results of these phase IIb studies are summarized in Table 1.

Table 1: Summary of Phase IIb Clinical Results

	AECB			CAP		Sinusitis		
	150 mg	300 mg	600 mg	300 mg	600 mg	150 mg	300 mg	600 mg
<b>Clinical Cure</b>	87%	90%	90%	92%	80%	89%	83%	71%
<b>Eradication</b>								
-S. pneumo	84%	90%	100%	87%	100%	3/3	8/8	9/12
-H. flu	94%	89%	83%	100%	72%	3/5	7/7	5/7
-M. cat	80%	92%	91%	6/8	2/4	8/9	3/4	4/4
-Overall	86%	89%	92%	92%	79%	77%	96%	78%
<b>AEs</b>								
-Diarrhea	13%	12%	21%	12%	17%	6%	6%	17%
-Taste	6%	19%	29%	17%	26%	1%	14%	27%
-Nausea	7%	13%	30%	12%	21%	3%	12%	26%
-Vomiting	2%	3%	11%	8%	13%	1%	6%	17%

The primary conclusions of these studies were: a) adverse events at 300 mg and above were too high to support a commercially viable product b) there was no statistical difference between doses from an efficacy (cure or eradication) standpoint.

The decision was made to proceed forward into phase III with a 150 mg QD dosing strategy for all indications. The decision to pursue this strategy alone would have resulted in considerable risk stemming from a) a moderate risk of clinical failure in the relatively difficult-to-treat indications of CAP/sinusitis b) the risk that the entire package could be dismissed by ex-US regulatory agencies should either the CAP or sinusitis clinical data be substandard. Therefore, a backup strategy was added to the core program to mitigate this risk. The clinical program to NDA is summarized below.

Figure X: Summary of Clinical Strategy to NDA

Development of IV and OS formulations was initiated in late 1999. Phase I studies on the IV formulation will be initiated X 2000; phase I studies on the OS formulation will be initiated June 2000.

The NDA filing for ABT-773 tablets is expected in December 2001 with an anticipated US market launch of December 2002. The IV and OS NDA filings are expected in December 2002 with an anticipated US market launch of December 2003.

### III. MARKET OVERVIEW

#### A. Epidemiology

Table 1: U.S. Prevalence of Bacterial Diseases by Diagnosis-MM

Otitis media	Sinusitis	Pharyngitis	Pneumonia	AECB
18.2	40.4	10.6	2.5	17.7

#### B. Market Data

Table 2: 1995-1999 U.S. Antibiotic Market

		1995	1996	1997	1998	1999	CAGR <sub>95-99</sub>	
U.S.	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

The U.S. tab/cap, oral suspension, and I.V. markets had 1999 sales of \$5.7B, \$1.1B, and \$2.1B respectively. Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics (approximately 30MM fewer generic antibiotic prescriptions were written in 1999 than in 1995). So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

**Table 3: 1999 U.S. Tab/Cap Antibiotic Market-Sales and TRX**

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	35.1	16.3%	20.8%
Blaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.0%	0.4	0.2%	59.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$590.5	10.3%	-1.1%	50.4	27.3%	-4.1%
<b>TOTAL TAB/CAP</b>	<b>\$5,715.4</b>	<b>100.0%</b>	<b>8.9%</b>	<b>221.5</b>	<b>100.0%</b>	<b>0.1%</b>

Table 3 shows 1999 tab/cap sales and prescriptions by class/product. Macrolides, fueled largely by gains in Zithromax, and quinolones, fueled largely by gains in Levaquin, have done very well in terms of both prescriptions and sales. The growth of these classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin. Zithromax prescriptions sales are closing in on the sales leader Cipro and far outnumber those of other competitors. Increasingly, the RTI market is coming to be dominated by two antibiotic classes, macrolides and quinolones. Quinolones have been able to leverage their activity against resistant Strep. pneumoniae and H. influenzae to become direct competitors to macrolides in the RTI market; a number of new entrants (moxifloxacin, gatifloxacin, gemifloxacin) will add to the competitive pressure. In essence, the market is being asked to make trade-offs between the real or perceived weaknesses of the macrolides (H. influenzae, resistant Strep. pneumoniae, GI events [clarif]) against those of the quinolones (safety, too broad spectrum, potential for resistance development).

**Table 4: 1999 U.S. Oral Suspension Antibiotic Market**

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$61.5	5.5%	-10.5%	26.7	43.9%	-7.1%
Cephs	\$375.7	33.5%	-10.8%	11.5	18.9%	-11.4%
Cefzil	\$168.3	15.0%	8.0%	3.9	6.4%	4.1%
Other Cephs	\$207.4	18.5%	-18.4%	7.6	12.5%	-16.0%
Ext. Spec. Macrolides	\$250.4	22.4%	30.9%	8.5	14.0%	39.1%
Blaxin	\$66.0	5.9%	-3.1%	1.6	2.6%	-7.0%
Zithromax	\$184.5	16.5%	108.6%	6.9	11.4%	165.3%
Augmentin	\$382.3	34.1%	17.2%	7.9	13.0%	10.2%
Other Classes	\$50.0	4.5%	-15.9%	6.2	10.1%	-18.3%
<b>TOTAL PEDIATRIC</b>	<b>\$1,119.8</b>	<b>100.0%</b>	<b>1.0%</b>	<b>60.8</b>	<b>100.0%</b>	<b>-5.4%</b>

Table 4 shows 1999 U.S. pediatric antibiotic sales and prescriptions by class/product. Augmentin, Zithromax and Cefzil are the market leaders, all of which have grown over the 1995-1999 period.



**Table 5: 1999 U.S. I.V. Antibiotic Market**

The following table shows 1999 U.S. I.V. antibiotic sales. Sales of I.V. antibiotic products have grown slightly as more expensive branded agents (Rocephin, Levaquin) have replaced lower cost generic agents. Rocephin, the market leader, had 1999 sales of \$514MM.

	Sales		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$69.1	3.3%	-3.6%
Carbapenem/Primaxin	\$139.3	6.6%	4.4%
Vancomycin	\$73.7	3.5%	-1.1%
Cephalosporins	\$904.9	42.7%	-1.9%
Rocephin	\$514.3	24.3%	4.0%
Other Cephalosporins	\$390.6	18.5%	-7.6%
Ery & Macrolides	\$45.5	2.2%	8.8%
Ext. Spec. Macrolides	\$35.3	1.7%	NA
Zithromax	\$35.3	1.7%	NA
Monobactams	\$331.4	15.7%	1.2%
Aminoglycosides	\$63.3	3.0%	1.7%
Quinolones	\$340.5	16.1%	21.4%
Cipro	\$120.5	5.7%	NA
Trovan	\$35.6	1.7%	NA
Levaquin	\$178.7	8.4%	NA
Other Classes	\$113.7	5.4%	21.5%
TOTAL I.V.	\$2,116.8	100.0%	3.2%

### C. Key Market Drivers

- Resistance to antibiotics will continue to increase. Physicians will be urged to restrict the use of antibiotics for documented, severe infections and to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant pathogens (Levaquin's recent claim for penicillin resistant *S. pneumoniae*) and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, etc) may confer competitive advantage to such agents.
- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs. The performance of recent quinolones along two dimensions may have a profound impact on the success of this class in the community RTI market: a) safety and b) development of quinolone resistance
- Convenience attributes such as QD dosing and short course of therapy (5-7 days) will become commonplace and will offer little in the way of differentiation; adverse event profiles and drug-drug interactions, however, are areas where improvements may be made.
- Unmet need in the antibiotic market is very low. Differentiation along current product attributes (clinical success, safety, convenience) will be difficult. Hence, companies will turn to new efficacy metrics as a means of differentiating their products. Efficacy toward resistant organisms will be an important new metric. PK/PD parameters will also be exploited to gain competitive advantage.

- Several key branded antibiotics will lose patent exclusivity over the next three to five years (see Table 6). Among those products losing patent exclusivity are the top three pediatric brands (Augmentin, Cefzil, Zithromax). While the influx of generic competition may result in increasing price sensitivity, the extent of the price sensitivity may be dampened in comparison to other markets where products do not lose their activity over time like antibiotics.

**Table 6: Anticipated Loss of Patent Exclusivity**

Augmentin	2002
Ceftin	2003
Cipro	2003
Dynabac	2003
Blaxin	2005
Cefzil	2005
Levaquin	2005
Zithromax	2005

- Antiviral therapeutics and diagnostics for influenza and colds will reach the market. While initial data suggest such agents may instead be used in an additive mode to antibiotics, increasing promotional support of such agents or a market increase in antibiotic resistance could alter this algorithm.

**D. Customers**

The bulk of antibiotic prescriptions are written by primary care physicians (GP, FP, IM, DO and Peds) and as such these physicians are the primary target market. Several specialties are also important, particularly from the standpoint of opinion development; these include infectious disease specialists, otolaryngologists (ENTs), allergists, and pulmonologists. Managed care is also a key customer, and strategies are being implemented to ensure the highest degree of formulary acceptance.

**E. Competitive Analysis**

Three classes of antibiotics represent the majority of the competition within the antibiotic market, namely ketolides, macrolides, and quinolones.

Whereas quinolones were once regarded as agents to be used only in cases of severe and/or non-respiratory infections, improvements in the safety and spectrum of these agents has allowed for increasing penetration into the community-acquired respiratory market. Two new quinolones, Tequin (gatifloxacin, BMS) and Avelox (moxifloxacin, Bayer) were launched in the U.S. in December 1999; a third, Factive (gemifloxacin, SKB) was filed with the FDA in December 1999. Beyond being highly competitive products from a product profile standpoint, the companies are also aggressively promoting these agents, each factor adding considerably to the competitive intensity within the community-acquired respiratory market. Tequin has fared well since its launch, outpacing the launch of the quinolone Levaquin by approximately X%. Quinolones are among the most active anti-infective classes in terms of number of compounds in development. Notable quinolones in development are T-3811 (Toyama/BMS), XXX, and XXX.

Macrolides are regarded as extremely safe and efficacious agents, but resistance to these agents, particularly with *Strep. pneumoniae*, is becoming more widespread. At the present time, resistance to macrolides is observed primarily in the context of in-vitro-based surveillance studies and has not yet resulted in a large number of clinical failures. Over time, however, macrolide resistance will reach a point that the clinical utility of these agents will be compromised.

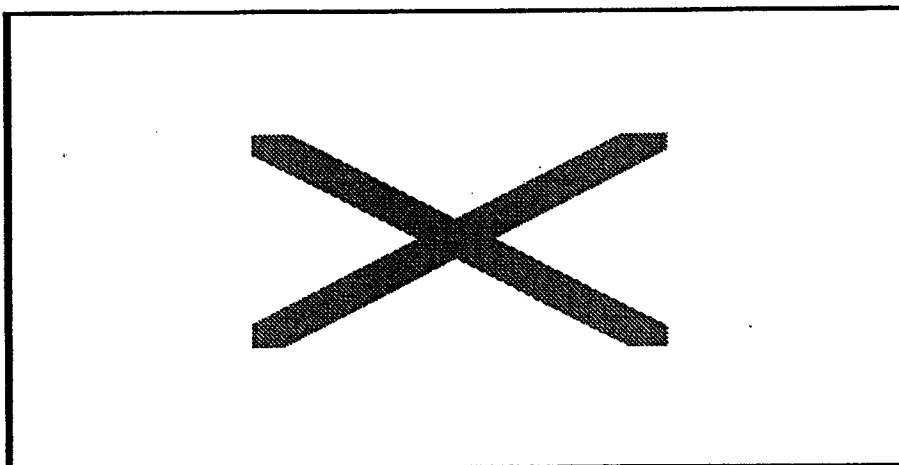
The response to this shortcoming of the macrolides are ketolides. Based on a macrolide structure, ketolides have improved microbiological activity against *Strep. pneumoniae* due to enhanced interactions with the ribosome. Ketek (telithromycin, Aventis) was filed with the FDA in March 2000, and will therefore likely be the first ketolide to reach the market. This first-to-market advantage may be relatively minor, however, as competitive intelligence has revealed limitations with the product including a relatively large dose (2 x 400 mg QD) and high COGS (which may limit its positioning flexibility). Scientific data presented at ICAAC 2000 also reported a high level of diarrhea (10-20%, see Appendix X for a full Ketek summary).

Zyvox (linezolid, Pharmacia), which represents the first agent of another novel class, oxazolidinones, was approved in the U.S. in April 2000. Zyvox has good coverage of Gram-positive pathogens such as *Strep. pneumoniae* and VRE but limited coverage of Gram-negative

and common community pathogens *H. influenzae* and *M. catarrhalis*. As such, placement of this product for community respiratory infections will be a challenge. Bayer and Zeneca are also pursuing oxazolidinones for anti-infective application in addition to Pharmacia.

A summary of the key emerging products is shown in Table 8.

**Table 8: Summary of Key Emerging Competitors**





#### IV. UNMET NEEDS

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, and this will likely continue and intensify over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation.

**Table 9: Unmet Needs in Anti-Infective Market**

Unmet Need	Pipeline Impact
Appropriate spectrum	As resistance continues to be an issue, the goal will be to match the spectrum of activity with the infections being treated. Macrolides have an appropriate RTI spectrum, but suffer from relatively poor activity against <i>H. influenzae</i> , a key respiratory pathogen. Quinolones cover the RTI spectrum, but are regarded by many to be too broad, also having activity against non-RTI Gram-negatives and anaerobic species.
Activity against resistant organisms	<i>S. pneumoniae</i> , MRSA, and VRE represent most problematic pathogens, though MRSA/VRE are not major community pathogens; efficacy against some G (-) pathogens (e.g. <i>Pseudomonas</i> ) is also becoming problematic. Most agents in pipeline offer increased efficacy against some resistant organisms but not others. Resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. It is unclear how quickly resistance will build to new classes of drugs. Gatifloxacin is touting that its 8-methoxy sidechain results in lower rates of resistance development; the role of PK profile in the development of resistance is also an emerging concept.
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)
Increased tolerability	Key areas remain GI and taste perversion (macrolide/ketolide) and QT prolongation (macrolide/quinolone). As the market continues to mature, the market will be less tolerant of any significant level of AE.
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact to varying degrees with other drugs; a potent drug with no interactions would be a benefit in this market

#### V. PRODUCT PROFILE

The product profile shown below compares the optimal product attributes with those of ABT-773. The performance of ABT-773 for many of these attributes has not yet been determined. This profile is based largely on product attributes the current market values and promotes. As better and better agents reach the market, the marketing significance of many of these attributes will decrease and will no longer serve to differentiate products. Efforts are underway to identify

new and relevant product attributes that would confer competitive advantage to ABT-773 (see section VII).

**Table 10: Optimal Product Profile Versus Actual**

<b>Optimal Product Attribute</b>	<b>Actual</b>	<b>Impact/Comments</b>
Improved activity against G+ and atypical pathogens vs clarit	Same	Better activity than quinolones
H. flu activity comparable to moxifloxacin	Improved vs clarit/azi; inferior to moxi	Issue can be mitigated with clinical data and favorable tissue concentration data
Indication for drug resistant S. pneumo*	TBD	M

## VI. PRODUCT OBJECTIVE, POSITION, & MESSAGE

Two poles to market: safety/convenience vs efficacy

Market convergence

2<sup>nd</sup> tier differentiators i.e. ribosomes, pack strategy

Maximization of profit to the anti-infective franchise is the objective. This will be effected through an optimal positioning of all the agents in the franchise, including ABT-773, Biaxin, Biaxin XL, and any future product additions. This is not necessarily the positioning strategy that will result in the highest combined product share.

Product positioning is simply an identification of the differentiating characteristics of a product followed by the marketing (positioning) of the product to the market segment(s) that value those characteristics. The "box" strategy has been a useful construct in segmenting the current antibiotic market for Biaxin. This "box" strategy is based on marketing research that indicated that the severity of the illness usually was the most significant driver of antibiotic selection for physicians. For less severe "box 2" infections (which may actually be viral), convenience and cost are the main drivers of selection, with efficacy secondary. For more severe "box 3" infections, efficacy drives the decision, followed by convenience and cost. The marketing research also revealed that physicians perceived Biaxin to offer a high degree of efficacy. The "box" strategy was simply a realization of the differentiating characteristics of Biaxin (efficacy) and the promotion of that feature to the segment that valued it.

What must first be determined is whether the "box" (i.e. severity-based) segmentation will still be relevant to the market of 2003. If this "box" segmentation remains relevant, the differentiating characteristics of ABT-773 relative to this segmentation must then be assessed. Based on what is currently known of ABT-773, it will likely not be differentiated from other competitors based on convenience attributes. As such, it would be difficult to position the product as a pure "box 2" agent. The only other option would be to position the product along efficacy dimensions. The challenge here is that it is becoming increasingly difficult to differentiate products along current efficacy metrics such as clinical success, eradication, and spectrum of activity.

Over the next several months, New Product Development will be working with Venture and Marketing to define a "wish list" of potential differentiating clinical outcomes to allow positioning flexibility. These outcomes will then be evaluated in marketing research along with various positioning strategies (position, message, price). The scenario that affords the highest return to the franchise will form the basis for the positioning strategy for ABT-773. This research will also form the basis for the phase III clinical trial plan.

## VII. KEY COMMERCIAL ISSUES & OPPORTUNITIES

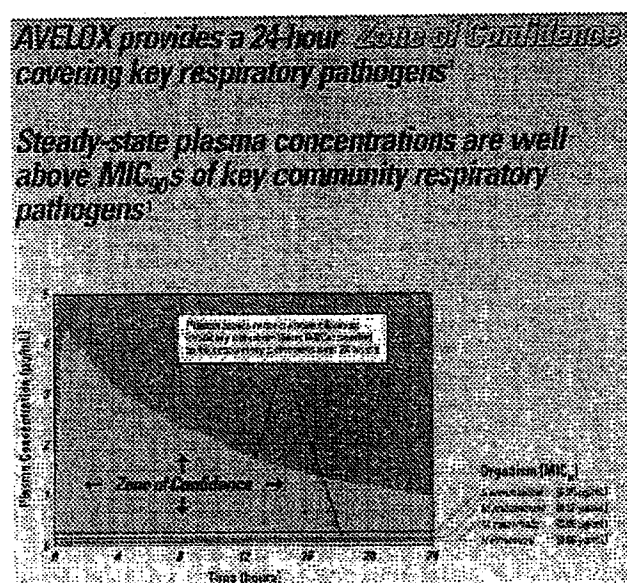
### A. ISSUES

#### Issue #1

Uncertainty in ABT-773 convenience profile i.e. potential for BID dosing

#### Issue #2

PK Profile (both serum and tissue)



#### Issue #2

Product Differentiation

#### Implication

At one time it was possible to differentiate antimicrobial agents through differences in key product attributes such as clinical efficacy, spectrum of coverage, dosing convenience and adverse events. Agents now reaching the market, however, are virtually identical with respect to these attributes, making product differentiation extremely difficult; this will be even truer when ABT-773 launches in 2003 (Table 11). Other sources of product differentiation beyond the traditional product attributes must therefore be identified and exploited.

#### Objective

Identify new metrics for product differentiation for ABT-773



### Strategies

Pharmacokinetic and pharmacodynamic (PK/PD) data is starting to emerge as a new source of product differentiation. It appears that moxifloxacin and gemifloxacin are both employing this strategy to differentiate themselves from other quinolones as well as from agents in other classes. The impact of these strategies should be taken very seriously given that 1) both Bayer and SKB are experienced players in the AIF market 2) they each employ a large number of sales representatives in the AIF market 3) the concepts put forth by the companies are virtually identical, in effect "colluding" to distance themselves from the crowded AIF market. A similar PK/PD strategy should be adopted for ABT-773 as well, at a minimum to neutralize any competitive advantage that could be realized by the competition (mainly the quinolones) but ideally to identify characteristics of ABT-773 which could be used to gain competitive advantage in its own right. Specifically:

- Concentration-dependent killing (quinolones) may be promoted as an advantage to time-dependent killing (macrolides/ketolides), implying an advantage in speed/efficacy as well as with induction of resistance ("dead bugs can't mutate"). If possible, work should be carried out to show comparable and/or superior kill kinetics to the quinolones. Such data would be used in conjunction with a marketing effort to distance the ketolide class from the negative PK/PD perceptions of the macrolides.
- The ratio of area-under-curve (AUC) to MIC is increasingly being adopted as a predictor for clinical outcome; at issue is the extent to which this ratio could be used as a promotional tool. While this ratio is applicable only to agents with concentration-dependent killing, the risk is that with enough promotional noise from the quinolones, prescribing physicians could erroneously start to apply this concept to agents like ABT-773 whose ratios might appear inferior (even if irrelevant) to those of the quinolones. Work should be carried out to determine if this ratio has any applicability to ABT-773 so that any efforts to promote agents over ABT-773 on the basis of this (misapplied) parameter can be blunted.
- Identify other PK/PD parameters where ABT-773 would have an advantage and where a compelling argument could be put forth as to the relevance of that parameter to the treatment of respiratory infection. Beyond that, considerable effort will need to be invested in the infectious disease community (opinion leaders, clinical study leaders, etc) to gain buy-in on these concepts. This will require the coordination of the Abbott scientists, venture members, marketing, and external collaborators to identify and implement such parameters.

Potential sources of differentiation beyond PK/PD should also be investigated. These might include:

- "Lifestyle" clinical outcomes, such as symptom improvement scores and onset of symptom improvement
- Pharmacoeconomic outcomes
- Post-antibiotic-effect
- Other respiratory pathogens e.g. *B. pertussis*
- New means of presenting adverse events i.e. not only by frequency but by the clinical significance of the adverse event

Over the next several months, New Product Development will be working with Venture and Marketing to define a "wish list" of potential differentiating clinical outcomes to allow positioning flexibility. These outcomes will then be incorporated into a positioning study (see issue #2) to determine the value of these outcomes to the market. Those outcomes deemed to have a sufficiently high ROI will then be recommended for inclusion into the phase III clinical trial plan.

**Issue #2**

Optimal product positioning

**Implication**

The positioning of ABT-773 must be carried out not only in regard to the overall anti-infective market, but also with respect to Biaxin, Biaxin XL, and Omnicef. The goal of the positioning strategy should be to maximize profit to the franchise, which may not be the strategy that maximizes combined franchise product shares.

Product positioning will also impact the extent to which the ketolide class can sell itself as a new class of antibiotics rather than merely an extension of the macrolide class. A new class would see less resistance in terms of formulary acceptance and would allow the class to distance itself from some of the negative perceptions of the macrolide class (H. flu, bacteriostatic, macrolide resistance).

As described above, the clinical trial plan should ultimately support the product positioning.

**Strategies:**

Primary marketing research will be carried out to determine the strategy that maximizes profit to the franchise. The objective of this research would be to identify the positioning (position, message, price) that offers the highest profit return to the franchise in light of the competitive landscape. This work will be in progress from November 1999 through January 2000. The product positioning will drive the phase III clinical trial plan. It is anticipated that the phase III clinical plan will need to be completed by February 2000.

**Issue #3**

The HMR ketolide telithromycin (HMR-3647) may reach the market up to two years in advance of ABT-773

**Implications**

- The positioning that HMR adopts for their ketolide could impact the positioning of ABT-773. If the messages of Abbott and HMR are similar, it will be more difficult to create interest in ABT-773. Conversely, if the messages are vastly different, "believability" or confusion issues could exist.
- Any negative product characteristics of telithromycin could be perceived as "class" effects, thus impacting the perceptions of ABT-773.
- The extent to which HMR's ketolide is accepted on a given managed care formulary may initially limit ABT-773's acceptance until a subsequent formulary review is undertaken.
- Share gained by HMR represents share that ABT-773 may need to capture depending on relative positioning of the two products

**Strategies**

The strategy to address this issue consists of communication to the market as to advantages of ABT-773 over telithromycin (and other products). While this strategy will likely do little to reduce the uptake of telithromycin, it may facilitate the switching from telithromycin to ABT-773 once ABT-773 launches. Specific strategies include:

- Utilize competitive intelligence sources to obtain knowledge of product profile and positioning tactics
- Presentation of comparative information at scientific meetings, opinion leader advisories, and in journals
- Use of Abbott Medical Liaisons to disseminate information to key opinion leaders
- Work with PPD Managed Care to ensure that ABT-773 is well positioned within the managed care environment

**B. Opportunities****Opportunity #1**

Antimicrobial Resistance

**Implication**

Resistance is emerging as a key differentiating dimension in the antibiotic market. The differentiating potential of resistance can be further segmented along two dimensions: 1) ability of the agent to treat resistant pathogens 2) propensity for induced resistance with use of the agent. The extent to which ABT-773 performs along these two dimensions of resistance may translate into a competitive advantage over other agents.

**Objective**

Leverage the resistance profile of ABT-773 to gain competitive advantage

**Strategies**

- Gain an indication for drug-resistant Strep. pneumo, the most prevalent resistant respiratory pathogen. However, given that moxifloxacin will have this same indication (gatifloxacin and gemifloxacin may as well), this indication should be considered a required product characteristic rather than a source of competitive advantage.
- Conduct clinical and in-vitro comparisons between telithromycin, gemifloxacin, moxifloxacin, and gatifloxacin (among others) for drug resistant infections/organisms with the intent of showing comparable and/or superior efficacy to those agents.
- An Achilles' heel of the quinolones appears to be the relative ease with which pathogens (particularly Strep. pneumo) can develop resistance. Bacterial resistance to the quinolones, which was previously thought to occur only by means of gene mutation, was recently shown



to develop from a transferable plasmid, which may accelerate the rate of development of resistance to this class of antibiotics. Indeed, in-vitro data has shown it requires relatively few generations of a pathogen exposed to a quinolone before resistance is induced. Finally, it appears that the development of quinolone resistance may confer resistance to unrelated classes of antibiotics. An understanding of the mechanisms of quinolone resistance, the implications of that resistance to other antibiotic classes, surveillance data on the prevalence of mutations among strains of community pathogens, and related information should be obtained with the intent of using this information as part of a "counter-promotional" strategy. This could entail the building of awareness of such issues prior to launch via scientific meetings, advisories, etc. followed by true detailing efforts with this information upon launch.

#### **Opportunity #2**

Potential for I.V. and oral suspension (pediatric) formulations

#### **Implications**

While not currently funded, I.V. and oral suspension formulations represent an opportunity along several dimensions. Biacin is not available in I.V. and Biacin oral suspension has not been well accepted due to taste issues. Hence, these two formulations represent an opportunity for enhanced franchise visibility in two key channels, hospitals and pediatrics. An I.V. formulation can also result in greater access to hospital formularies and can pay dividends in greater tablet business stemming from I.V. step-down therapy. Beyond the incremental sales that an oral suspension formulation would provide, it also sends a strong signal to the market that the agent is safe. This will be an important part of the promotional strategy for competing with the quinolones, which have been unable to obtain pediatric indications because of various safety issues.

#### **Objective**

Develop I.V. and oral suspension formulations

#### **Strategies**

- Obtain funding for I.V. and oral suspension formulations for FY2000
- Develop the formulations in accordance with the product profiles shown in Section V

#### **Opportunity #3**

Exploiting a new product class-ribosome binding

#### **Implication**

The new ketolide class may result in a high interest level among the target market, including potentially greater access to managed care formularies.

#### **Objective**

Leverage the "new class" status to increase market awareness and acceptance

**Strategies**

- Presentation of comparative information at scientific meetings, opinion leader advisories, and in journals
- Use of Abbott Medical Liaisons to disseminate information to key opinion leaders
- Establish ABT-773 web page and, nearing and during launch of telithromycin, direct Biacin sales reps to distribute the web address as part of the Biacin sales call (Medical Regulatory must be consulted).
- Work with PPD Managed Care to ensure that ABT-773 is well positioned within the managed care environment

## **VIII. STRATEGIC MARKETING MIX**

### **PRODUCT:**

#### **A. USAN/Branding Strategy**

- Identification of generic name in progress; estimated completion 12/99. Candidate names will be filed with USAN, with approval approximately 12 months post-submission.
- Brand name creation initiated 8/99 with Interbrand. Objective is to identify a single global brand that will be used in all markets. Identification of candidate names for submission to Patent and Trademark Office 1Q2000. Brand name will also be registered as the website for ABT-773.
- The intent will be to utilize the brand name as much as possible for communications external to Abbott, e.g. advisories, scientific meetings, press releases, etc.

#### **B. Formulation Plan**

- ABT-773 will be available in a tablet; the goal is to have a QD formulation, which appears likely based on phase IIa and pharmacokinetic studies. Multiple tablet strengths may be available, pending phase IIb studies and marketing research/positioning studies.
- Funding for I.V. and oral suspension (pediatric) formulations has not yet been achieved. It is likely that these programs will be funded for FY2000. Development plans for these two formulations are being established as of this writing.

#### **C. Packaging**

- Determine value of a convenience pack strategy in light of ultimate product positioning

### **COMMUNICATION STRATEGY:**

#### **A. Professional**

The focus of the communication strategy is toward professionals. Activities currently ongoing in this arena include opinion leader development through advisories and "VIP" visits, posters/presentations at scientific meetings, and articles in journals. An ABT-773 Communication Strategy Group consisting of NPD, AI New Product Planning, and Venture representatives meets monthly to plan communication activities.

#### **B. Consumer**

No activities planned.

**C. Associations/Agencies**

While no activities are currently ongoing, work to identify agencies/organizations whose policies are consistent with the positioning of ABT-773, specifically with regard to resistance and appropriate use, will be initiated. The CDC and WHO are potential partners, both of whom have issued statements regarding appropriate use of antibiotics.

**D. Managed Care**

Work with managed care to develop pre-launch communication plan

**PRICING STRATEGY:**

This will be determined in the product positioning marketing research





## **Deposition Exhibit 4**

**P's Exhibit HZ**



Gregory  
Bosco/LAKE/PPRD/ABBOTT

09/13/2000 12:44 PM

To Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT  
cc George Aynilian/LAKE/PPRD/ABBOTT@ABBOTT  
bcc  
Subject ABT-773 Dev Plan

Carol,

Here's the PPD Regulatory piece. Jeanne has reviewed it.

Greg



Development Plan - 9-00.doc



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## D. Regulatory Strategy

## D.1 Regulatory Strategy SWOT Analysis

Table D.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<ul style="list-style-type: none"> <li>QO dosing may be viewed as positive for patient compliance if data is strong</li> <li>If the drug has a favorable risk benefit ratio with added value compared to existing therapies then the likelihood of approvability is high in EU countries or other countries requiring a CPMP package</li> <li>ABT-773 may present a key point of differentiation with promising activity against macrolide and penicillin resistant <i>Streptococcus pneumoniae</i> and enhanced antibacterial activity <i>in vitro</i>. If proven <i>in vivo</i>, this may indicate favourable relative therapeutic value required for approval and inclusion within local use guidelines.</li> </ul> <p>For COFs countries, if the US or EU receives approval then approvals in these LA/PAA countries are assured assuming appropriate sourcing.</p>	<p>Make sure PK/PD data is available to support dose selection rationale</p> <p>The development programs must be designed to unequivocally demonstrate the existence of an added value (e.g. safety or clinical efficacy against resistance species)</p> <p>To utilize the enhanced bacterial activity as a key point of differentiation need to:</p> <ul style="list-style-type: none"> <li>Ensure clinical program is designed to optimize chances of obtaining desired isolates</li> <li>Ensure appropriate pk/pd studies are performed</li> <li>Seek agreement from FDA regarding burden of proof for labeled indication against resistant pathogens</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>Take with food labeling is required to reduce AE's</li> <li>If BID is chosen for either CAP or ABS, diurnal variation may become an issue during FDA review</li> <li>Conformance to Abbott's &amp; FDA's Electronic Document Management System requirements may impact filing date</li> <li>High COG's for bulk drug driving vendor matrix and push to redefine starting material</li> </ul>	<p>FDA will still require pivotal bioavailability studies to be done in fasted state.</p> <p>Justification must be provided</p> <p>Electronic filing likely to be valued very highly by FDA, so need to manage internal process to see that we can meet requirements</p> <p>Need FDA buy-in from End-of-Phase 2 CMC meeting on starting material and vendor matrix, including stability requirements</p> <p>Communicate with team, international</p>

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	<p>Harmonization of global clinical trial designs and guidelines</p> <ul style="list-style-type: none"> <li>Differences in medical practice exist worldwide for antibiotics and associated infections</li> <li>Differences in comparator and dosing regimens</li> <li>Stringent EU regulatory environment with antibiotics</li> </ul> <p>EU filing will require a harmonized labeling therefore country-specific favourable labeling cannot be pursued (as done with clarithromycin)</p> <p>Two dose scenario with a lower dose chosen for ABSCB, Sinusitis and Pharyngitis with a second dose chosen for CAP may provide limited numbers to assess safety of the higher dose</p> <p>Increased resistance awareness may influence stricter requirements and trend away from lowest effective dose</p>	<p>affiliates, international experts and discuss with EU authorities through agency meetings to ensure design of trials and comparators are acceptable</p> <p>Discuss any country specific issues with authorities, international experts and affiliates. Monitor regulatory environment and competitive products.</p> <p>Discuss issue authorities at agency meeting and ensure MAA addresses this issue. May consider Phase IV studies to address this concern.</p> <p>Ensure clinical program includes relative pk/pd studies and can demonstrate clear efficacy at proposed doses. Ensure clinical program is designed to obtain resistance isolates</p>
<b>Opportunities</b>	<ul style="list-style-type: none"> <li>Labeling for resistant organisms if isolates are obtained</li> </ul> <p>Eligible for Centralised filing process which would provide EU-wide 10 year protection. May also file by Mutual Recognition procedure which more provides flexibility for non-harmonized disease practices (e.g. infectious disease/antibiotics)</p> <p>Once Daily Dosing may enhance compliance</p>	<p>Get agreement with FDA at End of Phase 2 meeting regarding number of isolates required for labeling claim</p> <p>Filing strategy to be determined based on strength of the clinical program and advice received from agencies during planned agency meetings</p>
<b>Threats</b>	<ul style="list-style-type: none"> <li>QT prolongation class labeling in Warnings section of labeling</li> <li>Liver enzyme increases in Warnings section of</li> </ul>	<p>Get agreement with FDA at End of Phase 2 meeting regarding EKG monitoring in Phase 3 and promote theory that QT prolongation is not class related</p> <p>Ensure that non-clinical and clinical program fulfill the CPMP points to consider on QTc prolongation.</p> <p>Ensure that non-clinical and clinical</p>

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	<p>labeling</p> <ul style="list-style-type: none"> <li>• Possible failure of short course therapy for Pharyngitis due to more stringent Test of Cure requirement from FDA</li> <li>• If gastrointestinal AE's are high, may affect benefit/risk assessment by FDA</li> <li>• Could be affected by CDC push to reduce antibiotic use; reserve use of drugs effective vs resistant organisms until existing therapies have failed</li> </ul>	<p>program addresses potential safety labeling issues and MAA/NDA addresses these concerns.</p>
--	--	---

## D.2 Registration Strategy and Timelines for Filing

Table D.2 Registration Strategy and Timelines for Submission		
REGION	Proposed Submission Date	Justification
US	<ul style="list-style-type: none"> <li>• August 2002</li> </ul>	Estimated completion of the clinical program and CMC stability data
<p>Europe</p> <p>Filing procedure (Centralised or MRP) to be determined based on strength of clinical data and discussion with authorities</p>	August 2002	Estimated completion of the chemistry/pharmacy and clinical data
<p>Japan</p> <p>Plan to bridge to US data assuming pk profile is similar in Japanese subjects and a successful Phase II bridging study is possible in Japan</p>	TBD	Bridging obviates the need for a lengthy and expensive Japanese Phase III program. Requires Kiku agreement.

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**D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program**

<b>Table D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program</b>				
<b>COUNTRY</b>	<b>Guideline Requirement</b>	<b>Probability of Achieving</b>	<b>Impact on Filing</b>	<b>Impact on Approvability</b>
<b>US</b>	• Draft Anti-Infective Guidances for CAP, ABECB, ABS & Pharyngitis	High	High	High
	• Draft Anti-Infective Guidances – General Considerations for Clinical Trials	High	High	High
	• Anti-Infective Points to Consider document	High	High	High
	• ICH Efficacy Guidances – E1 through E12	High	High	High
	• ICH Safety Guidances – S1 through S7	High	High	High
	• ICH Quality Guidances – Q1 through Q7	High	High	High
<b>Europe</b>	All ICH guidelines as above, plus CPMP points to consider on QT prolongation CPMP guideline on the clinical evaluation of antibacterials DRAFT CPMP guideline for pk/pd	High/Moderate	High	High
<b>Japan</b>	All ICH guidelines as above plus local guidelines/JP issues. ICH E5 ethnic bridging guideline.	Moderate/Unknown	High	High

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**D.4 Table of Proposed Discussions with Health Authorities**

<b>Table D.4 Table of Proposed Discussions with Health Authorities</b>		
<b>COUNTRY</b>	<b>Reason for Discussion</b>	<b>Proposed timing for Discussion</b>
<b>US</b>	<ul style="list-style-type: none"> <li>• End of Phase 2 -- Clinical</li> <li>• End of Phase 2 -- CMC</li> <li>• Pre-NDA -- Clinical</li> <li>• Pre-NDA -- CMC</li> </ul>	10/20/00 TBD TBD TBD
<b>Europe</b>	<ul style="list-style-type: none"> <li>• Individual agency meetings with UK, Germany, France and Spain to discuss Phase III Clinical program trial designs</li> <li>• Pre-filing meetings to be determined based on filing strategy</li> </ul>	UK complete -- 07/10/00 Germany complete- 07/21/00 France scheduled -- 08/30/00 Spain -- to be determined
<b>Japan</b>	<ul style="list-style-type: none"> <li>• KIKO- discuss bridging strategy to 300 mg EU/US program</li> <li>• KIKO -- re-discuss dose justification</li> </ul>	Complete -- June 2000 TBD

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## **Deposition Exhibit 5**

**P's Exhibit IF**



Jeanne M  
Fox/LAKE/PPRD/ABBOTT  
11/28/2000 09:27 AM

To Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT,  
Jerald J Wenker/LAKE/PPD/ABBOTT@ABBOTT,  
Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT, Rod  
M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Arthur J  
Higgins/LAKE/PPD/ABBOTT@ABBOTT, Linda J  
Swanson/LAKE/PPRD/ABBOTT@ABBOTT, Mike  
Rubison/LAKE/PPRD/ABBOTT@ABBOTT, Walid  
Awni/LAKE/PPRD/ABBOTT@ABBOTT  
John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Carl  
Craft/LAKE/PPRD/ABBOTT@ABBOTT, George  
Aynilian/LAKE/PPRD/ABBOTT@ABBOTT, Reid  
Patterson/LAKE/PPRD/ABBOTT@ABBOTT, David D  
Morris/LAKE/PPRD/ABBOTT@ABBOTT, Jie X  
cc Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Linda E  
Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Joaquin M  
Valdes/LAKE/PPRD/ABBOTT@ABBOTT, Maria M  
Paris/LAKE/PPRD/ABBOTT@ABBOTT, Carol S  
Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Gregory  
Bosco/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject Executive Summary of ABT-773 End-of-Phase 2 Mtg w/  
FDA

Yesterday (11/27) the Abbott people on the CC list met with FDA's Anti-Infective Division for the End-of-Phase 2 meeting on ABT-773. Prior to the meeting we had been placed on clinical hold in a teleconference last Monday (11/20). Following are the high points from yesterday's meeting. Detailed minutes of the meeting will be distributed at a later time.

The meeting was generally successful. FDA stated that we are no longer on clinical hold and may proceed with our Phase 3 trials. They have requested additional toxicology work be done to evaluate QT in dogs, but the study can be done concurrently with Phase 3 and they will consider study design proposals from Abbott. FDA accepted the design for the CAP and sinusitis dose-selection studies, although they suggested changes to the statistical analyses for these studies. While FDA acknowledged that our proposal for 15 resistant isolates/pathogen to support a claim for resistant organisms looked reasonable, they will need a good, solid body of evidence. They cautioned us that they have not seen a body of data that supports macrolide resistant *Strep pneumo* as a clinical concern. They also advised us that we would need to include bacteremic CAP patients with resistant pathogens in order to secure an indication, which would be difficult to do with an oral drug. The FDA reviewers provided a number of recommended protocol changes, most of which are minor to actual study conduct. In addition, we were directed to modify all of our informed consents to inform patients that QT prolongation has been seen with related classes of drugs and therefore may be a risk with ABT-773.

jeanne



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## **Deposition Exhibit 6**

**P's Exhibit IG**



Jeanne M  
Fox/LAKE/PPRD/ABBOTT  
11/29/2000 01:48 PM

Rod M Miltag/LAKE/PPD/ABBOTT@ABBOTT, Carl  
To: Craft/LAKE/PPRD/ABBOTT@ABBOTT, George  
Aynilian/LAKE/PPRD/ABBOTT@ABBOTT  
cc: Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT,  
Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject: Slides for 12/5 meeting

OK, here's my first draft of slides for the Leiden meeting. Please feel free to make comments or redirect me if you think I'm missing something. I guess I think after our meeting on Monday, the only major issues identified which are still open are QT, liver, and resistant pathogens, so that's what I focussed on with some general comments at the end.

jeanne

p.s I apologize for the separate files. I am obviously not as good on my PC as Rod is!



Leidenslides1.ppt Leidenslides2.ppt leidenslides3.ppt leidenslides4.ppt leidenslides5.ppt leidenslides6.ppt



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### ABT-773 Regulatory Status

- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting  
11/27/00
- End-of-Phase 2 CMC FDA meeting target  
1/01
- Tablet NDA submission target 8/02

### ABT-773 Regulatory Issues

- ABT-773 Potential for QT Prolongation
  - QT issue is hot button for FDA
  - Question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QT
  - Required to include ECG monitoring in pivotal Phase 3 studies

### ABT-773 Regulatory Issues

- ABT-773 Potential for QT Prolongation (continued)
  - telithromycin (Ketek) data residing at FDA
    - Advisory Meeting scheduled for January
- FDA may require a Phase 1 study in patients with underlying cardiac disease
- Some antimicrobials now contain warnings for QT prolongation

### ABT-773 Regulatory Issues

- ABT-773 Potential for Liver Toxicity
  - Ketolides similar to macrolides?
  - Request for additional dog tox work
  - telithromycin (Ketek) data residing at FDA
    - Advisory meeting scheduled for January
- Plan to conduct routine liver monitoring in all Phase 3 studies

### ABT-773 Regulatory Issues

- Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of “macrolide-resistant *S. pneumo*”
- FDA will require “body of evidence”
  - excellent eradication of susceptible organisms
  - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients



### ABT-773 Regulatory Issues

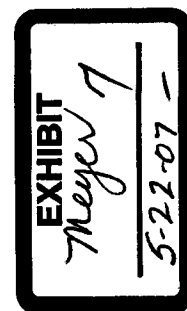
- Miscellaneous
  - Based on NDA timing, potential good candidate for E-submission
  - Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
  - Timing of pediatric program and “due diligence” for formulation development critical



## **Deposition Exhibit 7**

### **P's Exhibit II**

**ABT-773 Portfolio Review**  
December 5, 2000



## **Agenda**

### **Part 1: General Overview, Tablet**

- Introduction-Carl Craft (5 min)
- Executive Summary-George Aynilian (10 min)
- Anti-Infective Market/Commercial Rationale-Rod Mittag (15 min)
- Microbiology-Bob Flamm (20 min)
- Tablet Clinical Program
  - Phase II data-Joaquin Valdes (20 min)
  - Phase III clinical plan-Joaquin Valdes (10 min)
- SPD Summary-Ashok Bhatia (10 min)
- Tablet Key Issues
  - Analysis of QT/Liver data-Dave Morris (20 min)
  - PK profile-Linda Gustavson (10 min)
  - Regulatory-Jeanne Fox (10 min)
  - Timeline risk George Aynilian (5 min)
- Tablet Commercial Profile, Strategy & Financials-Rod Mittag (10 min)



**Agenda**  
**Part 2: I.V., Pediatric, Japan, Q&A**

- I.V. Program/Issues-Carol Meyer (5 min)
- Pediatric Program/Issues-Carol Meyer (5 min)
- Japan Program/Issues-Carol Meyer (5 min)
- ABT-492 (time permitting)
  - timeline
  - budget
  - rationale
- Summary-Carl Craft (5 min)
- Q&A

**ABT-773**  
***Executive Summary***

- **Management**
  - Established European Clinical Team (11 dedicated members)
  - Plans ongoing to strengthen Japan team
  - Completed staffing of Abbott Park team
  - Established communication team
  - Completed conceptual model of study tracking application (web based)
  - Established integrated project management system

**ABT-773**  
**Executive Summary**

- **Chemistry**
  - Exceeded '00 goals for yield, cost/Kg and deliveries
  - Task Force implemented modification of 3 steps
  - 3 TPMs for intermediates well established
  - Prepared package for justifying Step 5 as starting material

**ABT-773**  
***Executive Summary***

- **Tablet Formulation**

- Scale up operations at AP and IDC on target
- Linkage of materials between scales and sites being established by bioequivalency trials.
- NDA runs and stability were initiated for 08/02 filing.

**ABT-773**  
*Executive Summary*

- **IV Formulation**
  - Clinical supplies complete. Tox. program ongoing. Phase I planned for 1Q '01.
- **Pediatric formulation**
  - Phase I complete with two prototypes. After-taste an issue. Formula optimization required. Pro-drugs under consideration. No funding in '01 plan budget



**ABT-773**  
**Executive Summary**

- **Preclinical Safety**
  - Dog model (IV infusion) and Purkenje fiber studies completed as part of effect of drug on QTc. Additional study planned per EOPll meeting with FDA.
- **Molecular Biology**
  - Extensive work on ribosomal binding completed. Preliminary results published. Additional studies ongoing.

**ABT-773**  
**Executive Summary**

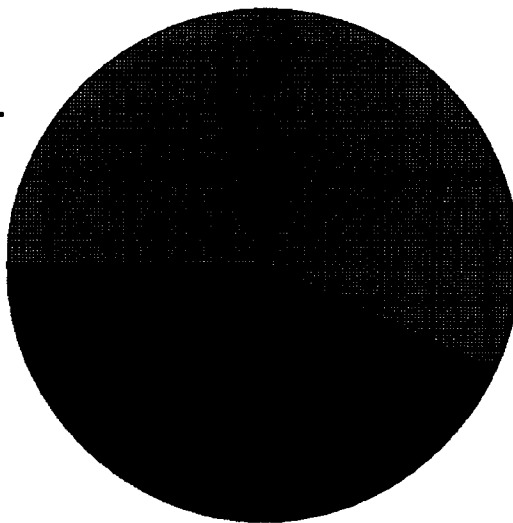
- **Clinicals**
  - Completed Three Phase IIb studies
  - Decision Support Analysis completed
  - Dose selection 150mg and 150mg bid
  - Initiated Phase III program( 6 studies, 4 under IND)
  - Completed all Investigator's meetings
  - Regulatory meetings
    - UK, Germany, France, US
- **End of Phase II package**
  - Document sent to FDA X/X
  - End of phase II meeting held with FDA 11/26
- **Japan bridging study/Kiko Mtg/Repeat Phase I in Japan**

**ABT-773**  
*Executive Summary*

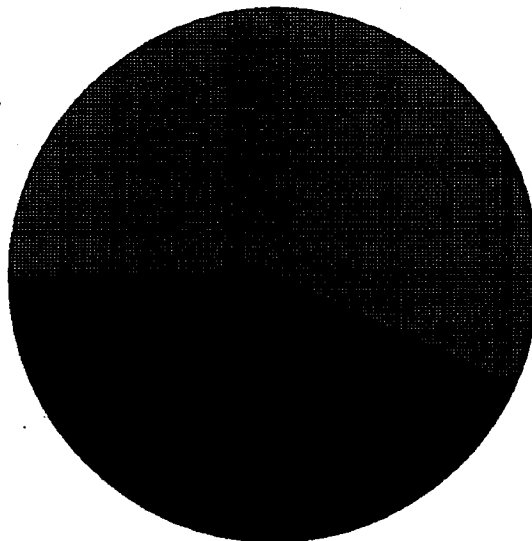
- **Key Events (Nov '00-June '01)**
  - Initiate Phase III (ABECB, ASP, ABS, CAP) in US/EU
  - End of Phase II meeting with FDA (New amendment, informed consent)
  - Initiate Japan Phase I program in Japan
  - Results of Phase III (CAP/ABS) studies
  - Selection of regimen between 150mg QD and 150mg BID for CAP/ABS.
  - Set up balance of Phase III studies (CAP/ABS) 4 studies

**Global Antibiotic Market Sales**  
*Current vs Future Projection*

**1999 Global Sales \$20.6B**



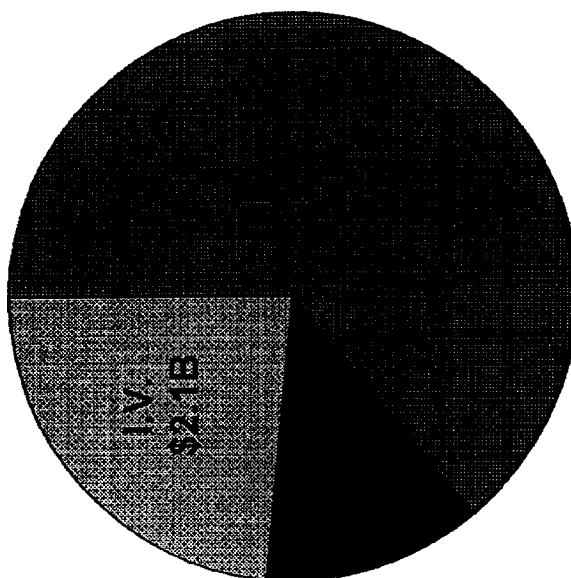
**2005 Global Sales \$25.3B**



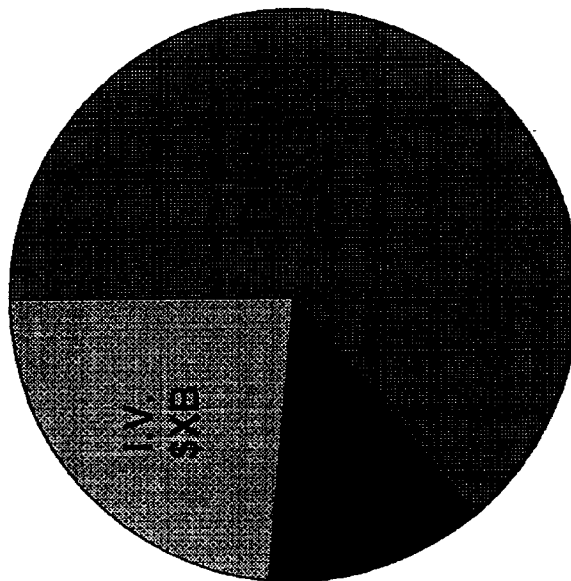
The antibiotic market is a large market and is expected to expand on a global sales basis

**Global Antibiotic Market Sales**  
*by Formulation*

**1999 U.S. Sales \$8.9B**



**1999 Ex-U.S. Sales \$11.7B**





# Key Competitors

## Ex-U.S. Market

	Franchise	Macrolides	Quinolones	Beta-Lactams	Infectables	Other
Abbott	\$ 717	\$879	\$ 22	\$ 3	\$ 12	\$ 30
Shionoi						
Selyaku	\$ 969	\$ 2	\$ 3	\$ 432	\$ 486	\$ 66
Pfizer	\$ 884	\$287	\$ 12	\$ 98	\$ 245	\$ 71
SKB	\$ 842	\$ 0	\$ 0	\$ 780	\$ 61	\$ 0
BMS	\$ 547	\$ 0	\$ 2	\$ 978	\$ 134	\$ 13
Roche	\$ 460	\$ 0	\$ 3	\$ 43	\$ 303	\$ 112
Bayer	\$ 524	\$ 0	\$437	\$ 43	\$ 43	\$ 1
Lilly	\$ 437	\$ 28	\$ 0	\$ 337	\$ 86	\$ 6
Fujisawa						
Yakuhin	\$ 522	\$ 0	\$ 0	\$ 411	\$ 131	\$ 0
Daiichi						
Selyaku	\$ 497	\$ 0	\$497	\$ 0	\$ 0	\$ 0
'98 Sub-Total	\$6,176	\$877	\$876	\$2,485	\$1,481	\$260

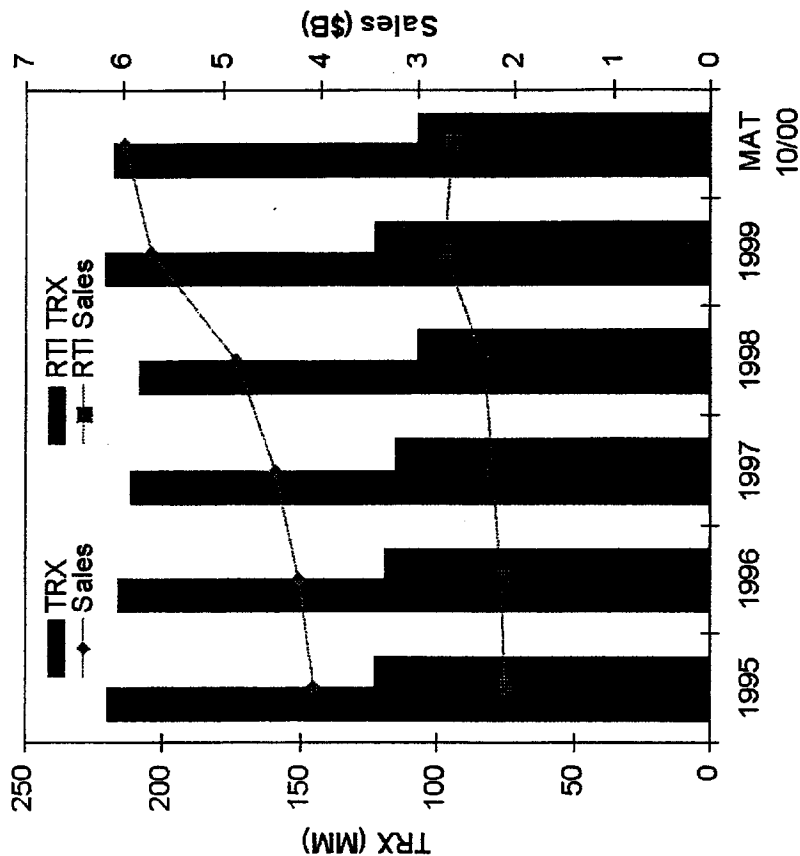
## U.S. Market

	Franchise	Macrolides	Quinolones	Beta-Lactams	Other	Infectables*
Abbott	\$956	\$740		\$48	\$3	\$165
Pfizer	\$1,386	\$1,076	\$71	\$3	\$3	\$213
SB	\$1,303			\$1,220		\$74
Bayer	\$1,034		\$811		\$1	\$122
J&J	\$797		\$612			\$185
Roche	\$526				\$10	\$516
Glaxo	\$551		\$6	\$425	\$28	\$92
BMS	\$387		\$1	\$386		
Lilly	\$107			\$33		\$74
Others	\$1,670	\$95	\$27	\$631	\$208	\$619
'98 Total	\$8,780	\$1,911	\$1,828	\$2,755	\$343	\$2,153
'98 Total	\$7,570	\$1,592	\$1,331	\$2,453	\$272	\$1,922
% Chg.	16.12%	20.06%	22.31%	12.31%	28.10%	12.02%
TY vs LY						

\* Includes IV form of all classes  
Source: IMS

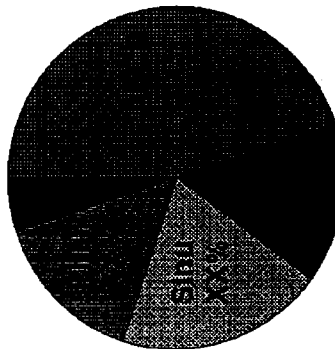
## U.S. Tab/Cap Antibiotic Market

### TRX & Sales Trends



- While negative pressure exists on antibiotic usage, market sales have increased substantially
- $TRX\ CAGR_{95-99} = + 0.1\%$
- $Sales\ CAGR_{95-99} = + 8.9\%$

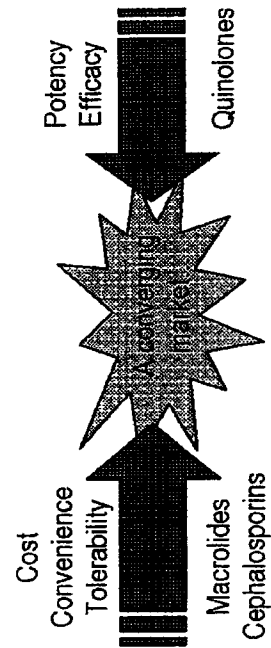
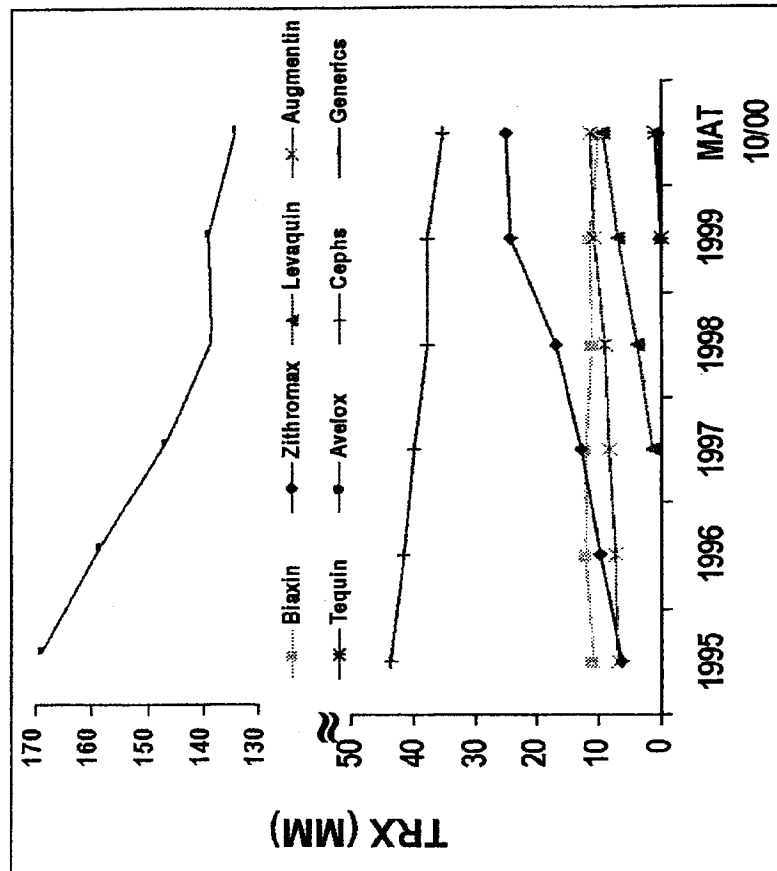
### RTI Sales by Indication



## U.S. Tab/Cap Antibiotic Market

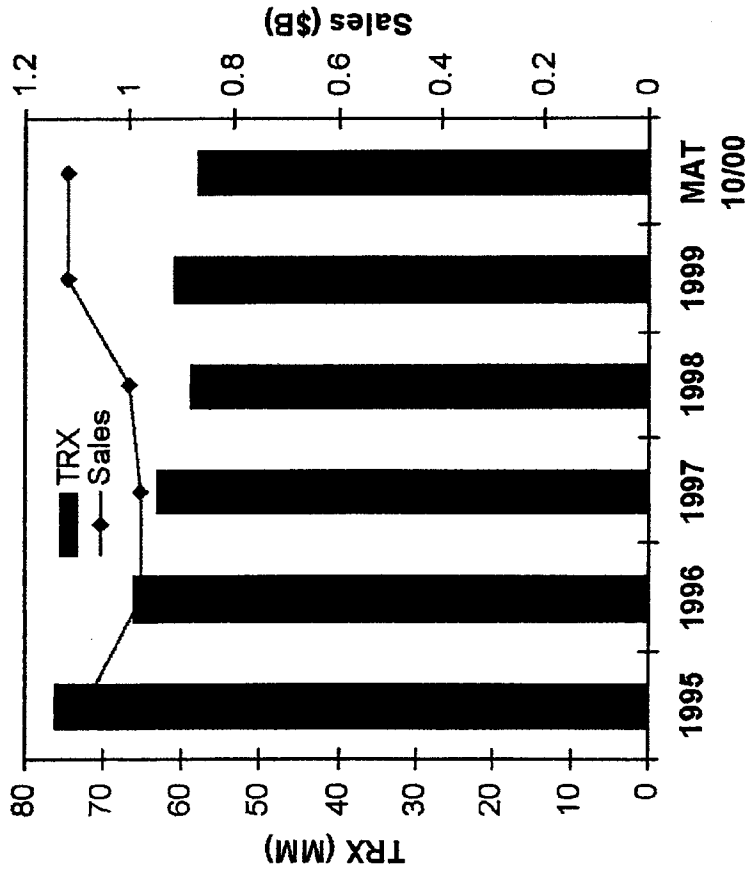
### Product Trends

- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Zithromax has driven market demand for cost/convenience/tolerability
- Quinolones (Levaquin, Tequin, Avelox) are fastest growing segment, playing into resistance concerns; 1998-99 growth of 15% (TRX) & 22% (\$)

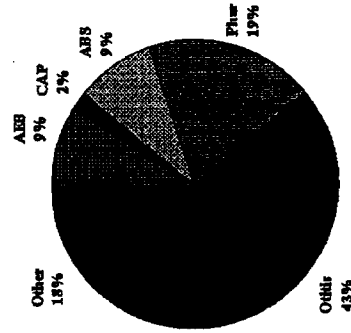


## U.S. Pediatric Antibiotic Market TRX & Sales Trends

- TRX CAGR<sub>95-99</sub> = - 5.4%
- Sales CAGR<sub>95-99</sub> = + 1.0%
- TRX under greater pressure than Tab/Cap market
- Recent leveling in sales



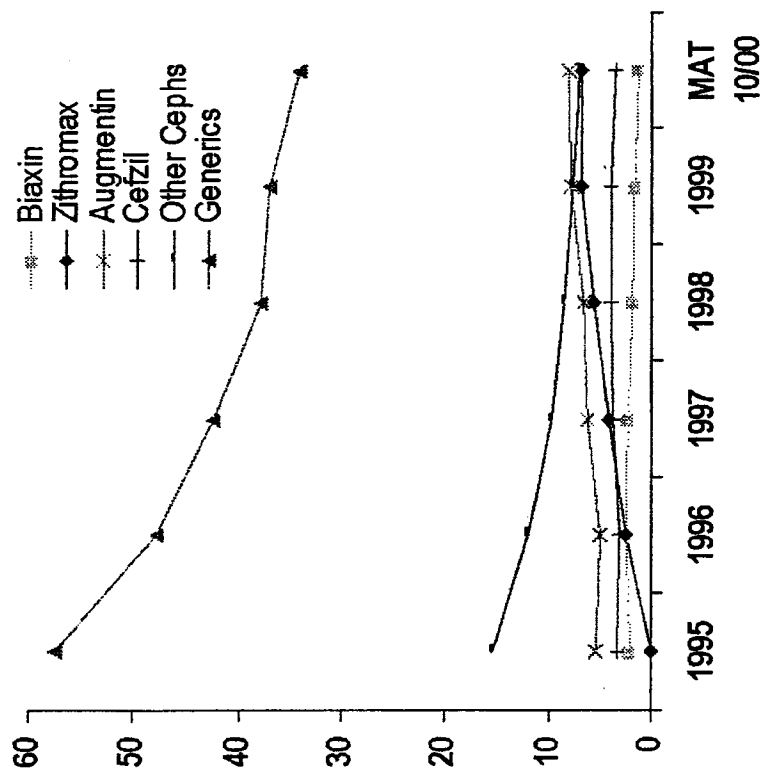
Sales by Indication



## ***U.S. Pediatric Antibiotic Market***

### ***Product Trends***

- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Taste and convenience are key market drivers
- Key branded products (Zithromax, Cefzil) lose patent exclusivity in 2005 timeframe
- May be opportunity for ABT-773, as resistance is substantial in this population; also conveys positive "safety" image to brand

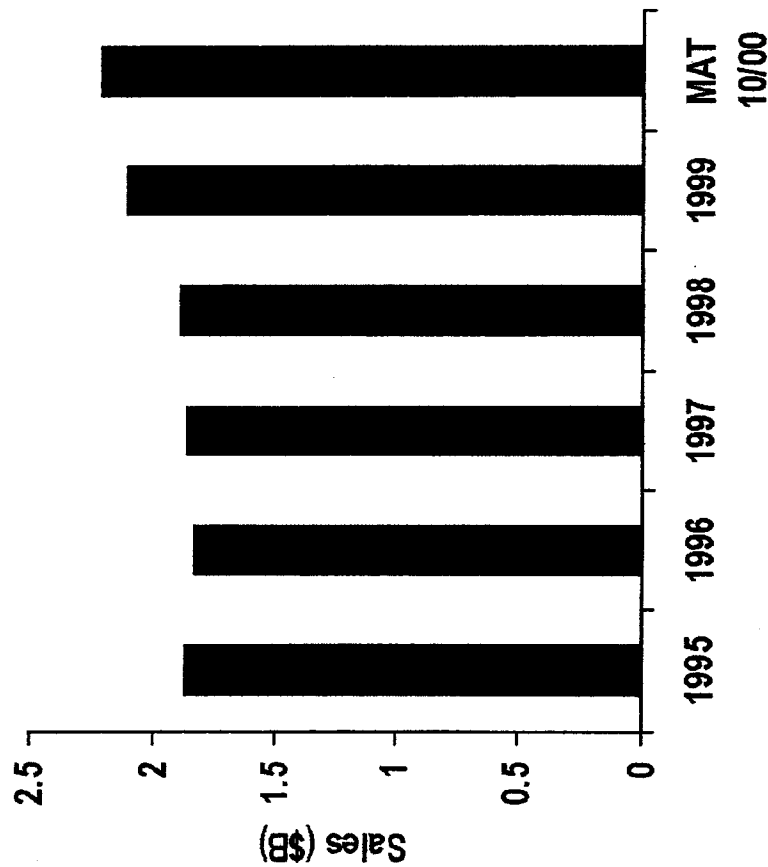
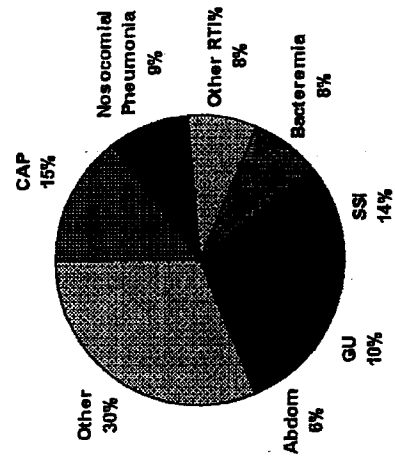


## ***U.S. Injectable Antibiotic Market***

### **Sales Trends**

- Current Market: \$2.1B, CAGR = + 3.2%
- Two market segments:
  - Severe community-acquired
    - Rocephin, Levaquin, Tequin, Zithromax
  - Nosocomial
    - Synecrid, Zyxox, vancomycin

**Uses by Indication**

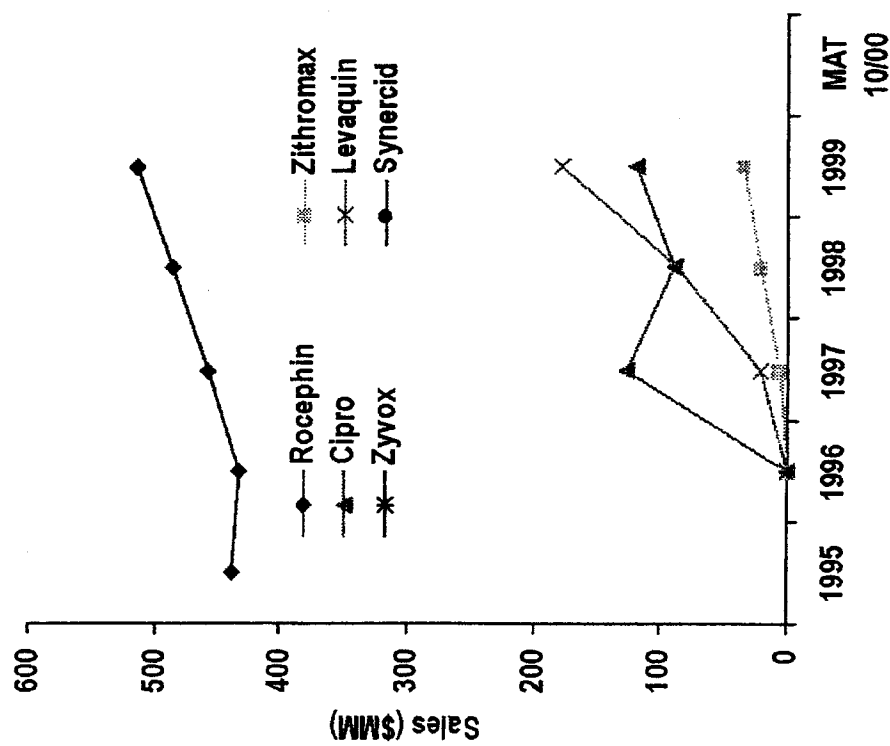




## U.S. Injectable Antibiotic Market

### Product Trends

- Rocephin is market leader, quinolones as class are making good gains
- Availability of I.V. has spill-over effect on tablet business
  - direct sales from step-down
  - enhances image of potency
  - more compelling package to managed care



## **Global Market Drivers**

### **Negative vs Positive Drivers**

- **Antibiotic Resistance**
  - Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓
  - Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑
- **Patent Expirations**
  - May increase price sensitivity and bargaining power of MCOs ↓
  - Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑
- **Market expansion ex-US** ↑
- **Unmet Need** ↓
  - Overall unmet need relatively low
  - Cost, convenience, tolerability take on added importance
  - Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics
- **Competition** ↓
  - 5 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox
  - Continued discovery/development activity by key competitors
  - High level of promotional activity

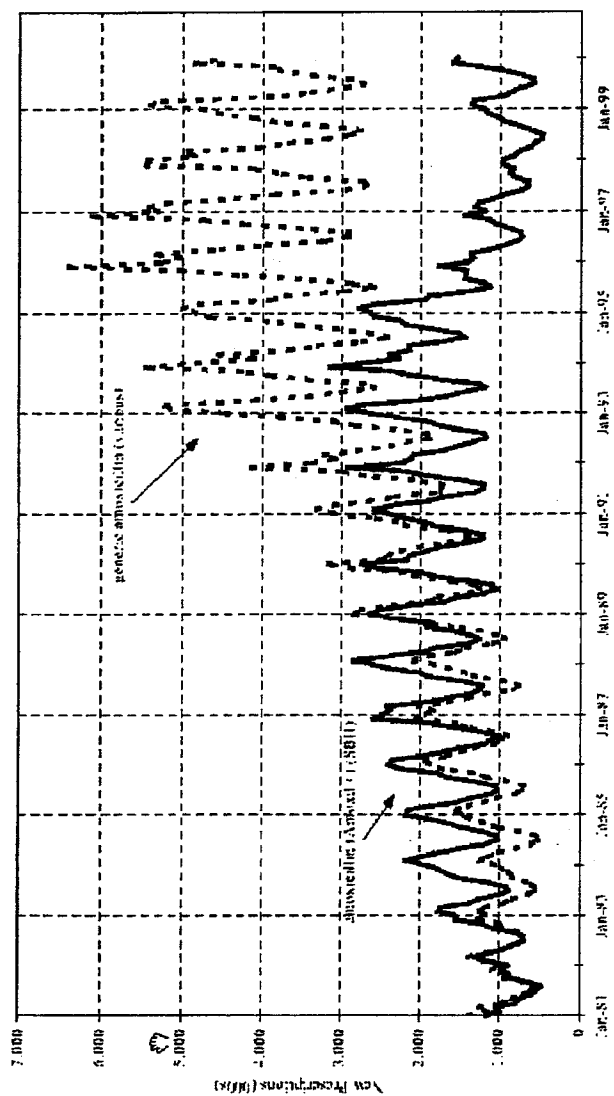
Negative driver ↓  
Positive driver ↑

• Resistance surveillance

***Patent Expirations***  
*Expiration & At Risk Sales*

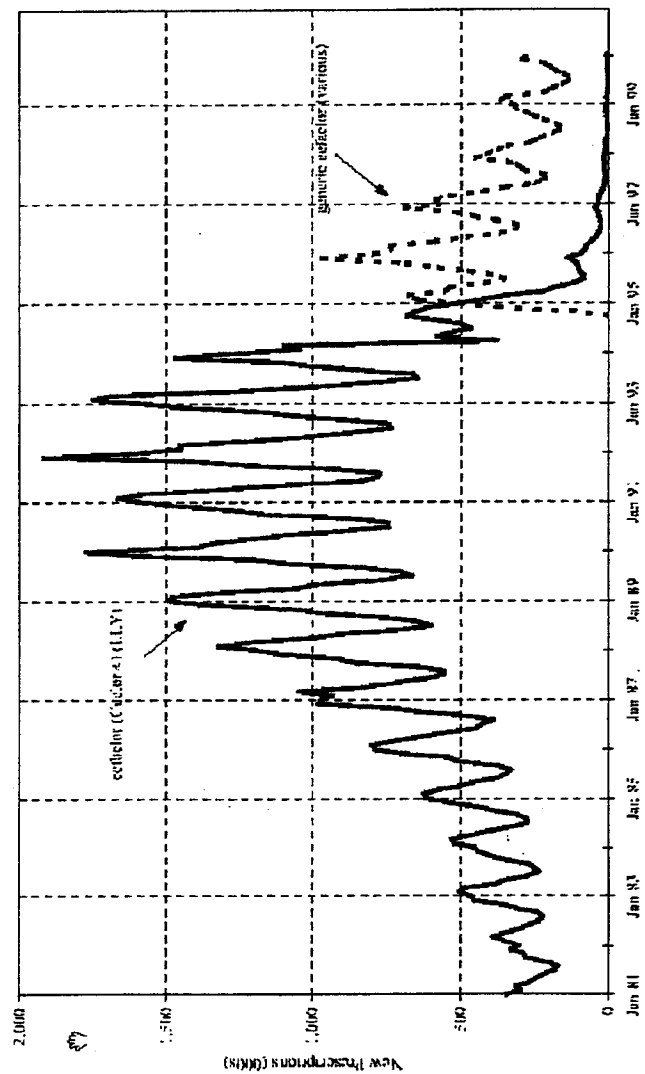
	<u>Year</u>	<u>1999 U.S. Sales</u> <u>(\$MM)</u>
Ceftin	2003	\$425
Cipro	2003	\$1,023
Biaxin	2005	\$756
Cefzil	2005	\$357
Levaquin	2005	\$708
Zithromax	2005	\$1,111
		\$5,540

Figure 139. SBH's Amoxiti® vs. generic amoxicillin, 1981-2000 (New Prescriptions, monthly data)



Source: IMS, U.S. prescription market. Retail only.

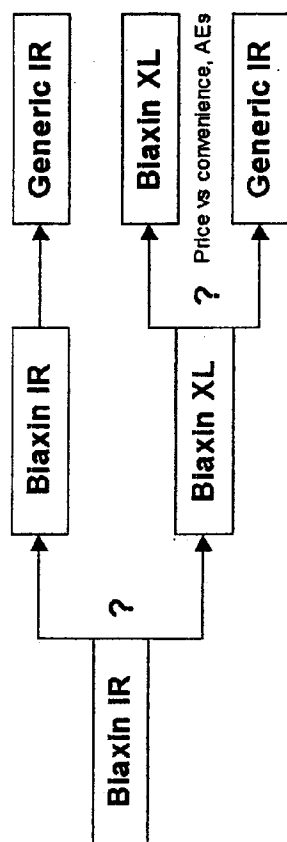
Figure 140. Lilly's Ceclor® vs. generic cefaclor, 1981-2000 (New Prescriptions, monthly data)



Source: IMS, U.S. prescription market. Retail only.



# **Biaxin Patent Expiration**

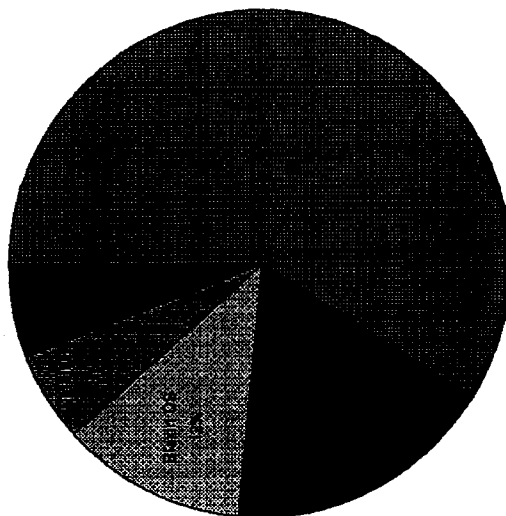


IR ==> XL Conversion	XL ==> Generic Conversion		
	Low	Med	High
Low	?	0	0
Med		?	0
High			?

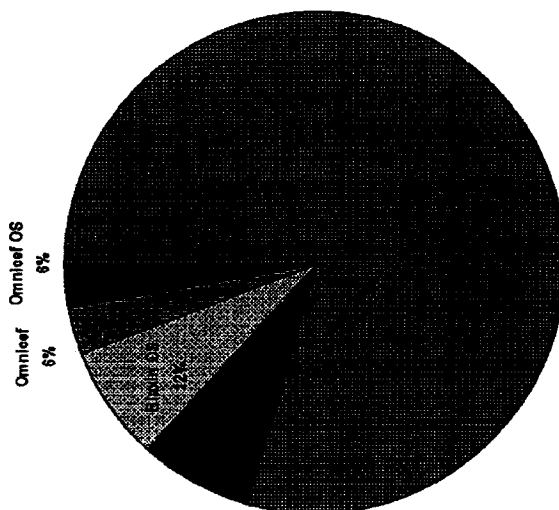
C = Convert Biaxin to ABT-773  
Assumes high conversion rate of IR  
to generics

# **Abbott Anti-Infective Franchise** 2001 Plan

**Ex-U.S. Sales = \$XXX MM**



**U.S. Sales = \$794 MM**



**The global Anti-Infective portfolio is heavily dependent upon Biaxin; ABT-773 represents a key program given the Biaxin patent expiration in 2005**

**ABT-773 Profile**

	<b>Current Profile</b>
<b>Dosing</b>	150 mg QD x 5 d for ABECB & pharyngitis (1-pack) 150 mg QD or BID x 10 d for CAP & ABS (2-pack if QD)
<b>Efficacy</b>	ABECB: 87% Cure, 86% Eradication (150 mg QD) ABS: 89% Cure, 77% Eradication (150 mg QD) CAP: XX% Cure, XX% Eradication (300 mg QD) Pharyngitis: No clinical data, need > 85% for indication
<b>Adverse Events (150 mg QD)</b>	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%
<b>Resistance Claim</b>	Being pursued, dependent on resistance prevalence/recovery/efficacy & availability of I.V.

# **ABT-773 Profile** **vs Biacin XL**

	ABT-773	Biacin XL
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: 6% Diarrhea: 6% Nausea: 3% Vomiting: 1%
Resistance Claim	Being pursued	Under exploration

## ***Key Commercial Challenges***

- **150 mg QD vs 150 mg BID**
  - 150 mg QD may prove efficacious in CAP/ABS ==> uniform QD dosing; however, limited 150 mg QD data currently exists, hence risk of BID dosing for CAP/ABS
  - Even if 150 mg QD efficacious, this regimen could receive regulatory challenge, particularly among ex-U.S. agencies==> QD and BID development programs, increased cost
- **PK**
  - Negative implications for efficacy as well as resistance development
- **H. flu eradication**
  - dose-defining pathogen, limited number of data points to date
  - a strength of quinolones
- **Tolerability may be sub-optimal**
  - diarrhea and taste perversion
- **2nd to market ketolide**
  - Aventis ketolide Ketek (telithromycin), FDA advisory 1/29





## ***Ketek Summary***

### ***Regulatory Status***

- Ketek (telithromycin, Aventis) will be first-to-market ketolide
- U.S.
  - Filed with FDA March 2000
  - FDA advisory 1/29
  - Expected approval 1Q01
- Ex-U.S.
  - Package submitted to EMEA as centralized filing in March 2000
    - Rapporteur = Sweden
    - Co-rapporteur = Portugal
    - Expected approval 1Q01
- Phase II in Japan (source: IMS World R&D Focus)

## **Ketek Summary**

### **Profile Summary**

- 800 mg QD for all indications
- AECB (5 d), CAP (7-10d), sinusitis (5d), pharyngitis (5d)
- High rate of diarrhea (10-20%), nausea (10%), but no taste perversion
  - statistically greater diarrhea vs trovafloxacin in phase III study
- Comparable levels of efficacy to comparators (see appendix for full clinical summary)
  - 74%-95% clinical cure
  - 69%-94% overall eradication
  - H. flu eradication is varied, with two CAP studies having 75% and 78% eradication; an AECB and sinusitis study had H. flu eradication of 88% and 100% respectively
- Liver function elevation
  - mentioned at ICAAC99, but Aventis claimed no clinically relevant impact at ICAAC2000; a CAP study references a 11.3% incidence of abnormal liver function, though the severity is unknown
- QTc prolongation: Aventis maintains no clinically relevant impact
- High COGS based on SPD pricing on intermediate
  - estimated telithromycin bulk drug cost of ~\$6,000/kg at launch vs \$3,000 for 773 at launch
  - may limit pricing flexibility
- Competitive intelligence suggests 14 penicillin resistant isolates submitted, same number as Levaquin (potential for pen-resistance claim, which Levaquin was granted)
  - eradication rate with these isolates unknown, important factor in FDA decision

# **Ketek Summary**

## **ABT-773 Comparison**

	<b>ABT-773</b>	<b>Ketek</b>
<b>Dosing</b>	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 400 mg QD ABECB: 5 d Phar: 5 d CAP: 7-10 d ABS: 10 d (or 5 d?)
<b>Efficacy</b>	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 86-89% Cure, 69-88% Erad ABS: 76-91% Cure, 86-91% Erad CAP: 91-93% Cure, 86-94% Erad Phar: 93-95% Cure, 84-91% Erad
<b>Adverse Events</b>	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: Not reported Diarrhea: 10-20% Nausea: 10% Liver, QTc: ???
<b>Resistance Claim</b>	Being pursued	Submitted in NDA

## **Ketek Summary**

### **ABT-773 Strengths/Weaknesses**

#### **ABT-773 Strengths vs Ketek**

- ABT-773 is considerably more potent than telithromycin against:
  - resistant and susceptible strains of *S. pneumo*
  - atypicals
  - *H. flu* (based on in vivo animal models)
- Lower rate of adverse events, particularly diarrhea
- 1 tab per dose vs 2
- Mechanistic advantages
  - faster binding to ribosome, slower release from ribosome, perhaps additional binding site(s)
- Potential for greater pricing flexibility

#### **ABT-773 Threats/Issues vs Ketek**

- 2nd to market
- Potential for BID dosing in CAP and/or sinusitis
- ABT-773 clinical/safety data at 150 mg QD based on relatively few data points
- PK profile

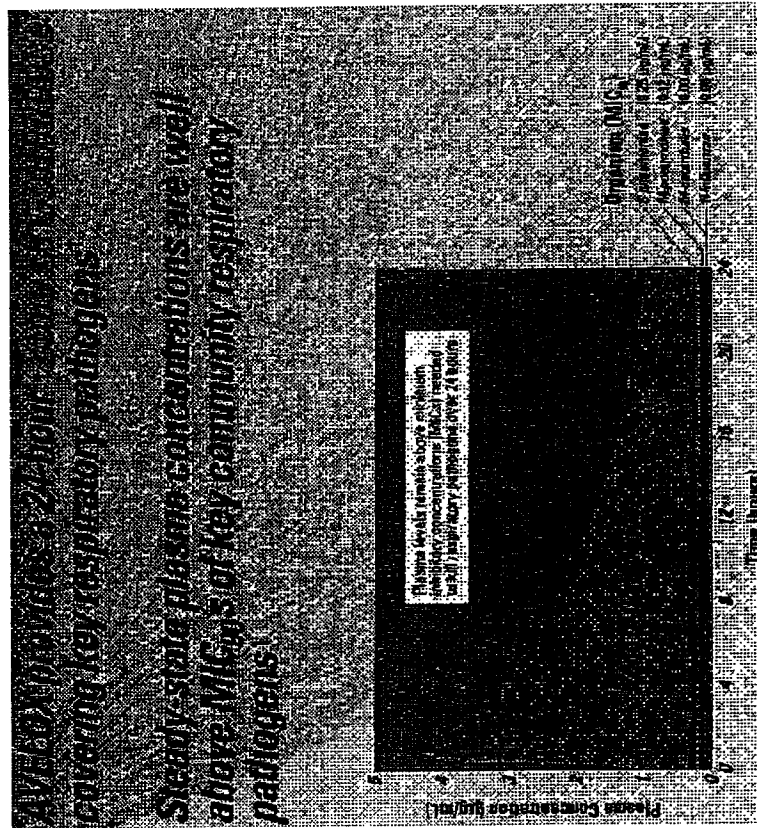
# Ketek Summary

## Clinical Data

Cure	91%		91%
Erection	91%		89%
Diarrhea	17%		6%
Neuro	11%		4%
Dizziness	5%		1%
Phosphatase #2	Ketek 800 mg QD x 5d	Pen V 500 mg QD x 10 d	NS
Cure	85%		84%
Erection	84%		83%
Diarrhea	12%		3%
Neuro	5%		1%
Dizziness	3%		1%
CAP #1	Ketek 800 mg QD x 10d	Pen V 500 mg QD x 10 d	
Cure	88%		89%
Erection	89%		85%
S. pneumoniae	94%		85%
H. flu	70%		60%
Diarrhea	5%		7%
Neuro	5%		5%
Dizziness	4%		2%
CAP #2	Ketek 800 mg QD x 7-10d	Impen 200 mg QD x 7-10d	
Cure	91%		95%
Erection	94%		100%
Diarrhea	17%(eiz)		6%
Neuro	5%		4%
Dizziness	2%		7%
CAP #3	Ketek 800 mg QD x 7-10d	Amoxicillin 1 g TD x 10 d	
Cure	95%		90%
Erection	86%		87%
S. pneumoniae	85%		85%
H. flu	75%		65%
Diarrhea	10%		6%
Neuro	6%		4%
Dizziness	NS		NS
CAP #4	Ketek 800 mg QD x 7-10d		Neuro
Cure	93%		-
Erection	89%		-
Diarrhea	5%		-
Neuro	5%		-
Dizziness	NS		-
Shingles #1	Ketek 800 mg QD x 10d	Acyclovir 800 mg TD x 10d	
Cure	74%		85%
Erection	69%		76%
Diarrhea	20%		24%
Neuro	NS		NS
Dizziness	NS		NS
Shingles #2	Ketek 800 mg QD x 5d	Ketek 800 mg QD x 10 d	
Cure	91%		91%
Erection	91%		91%
S. pneumoniae	93%		89%
H. flu	100%		85%
Diarrhea	10%		13%
Neuro	5%		7%
Dizziness	NS		NS
Shingles #3	Ketek 800 mg QD x 5d	Ketek 800 mg QD x 10 d	
Cure	86%		71%
Erection	86%		65%
Diarrhea	19%		20%
Neuro	12%		9%
Dizziness	5%		5%
Shingles #4	Acyclovir 800 mg TD x 10 d		
Cure	75%		75%
Erection	24%		24%
Diarrhea	8%		8%
Dizziness	2%		2%

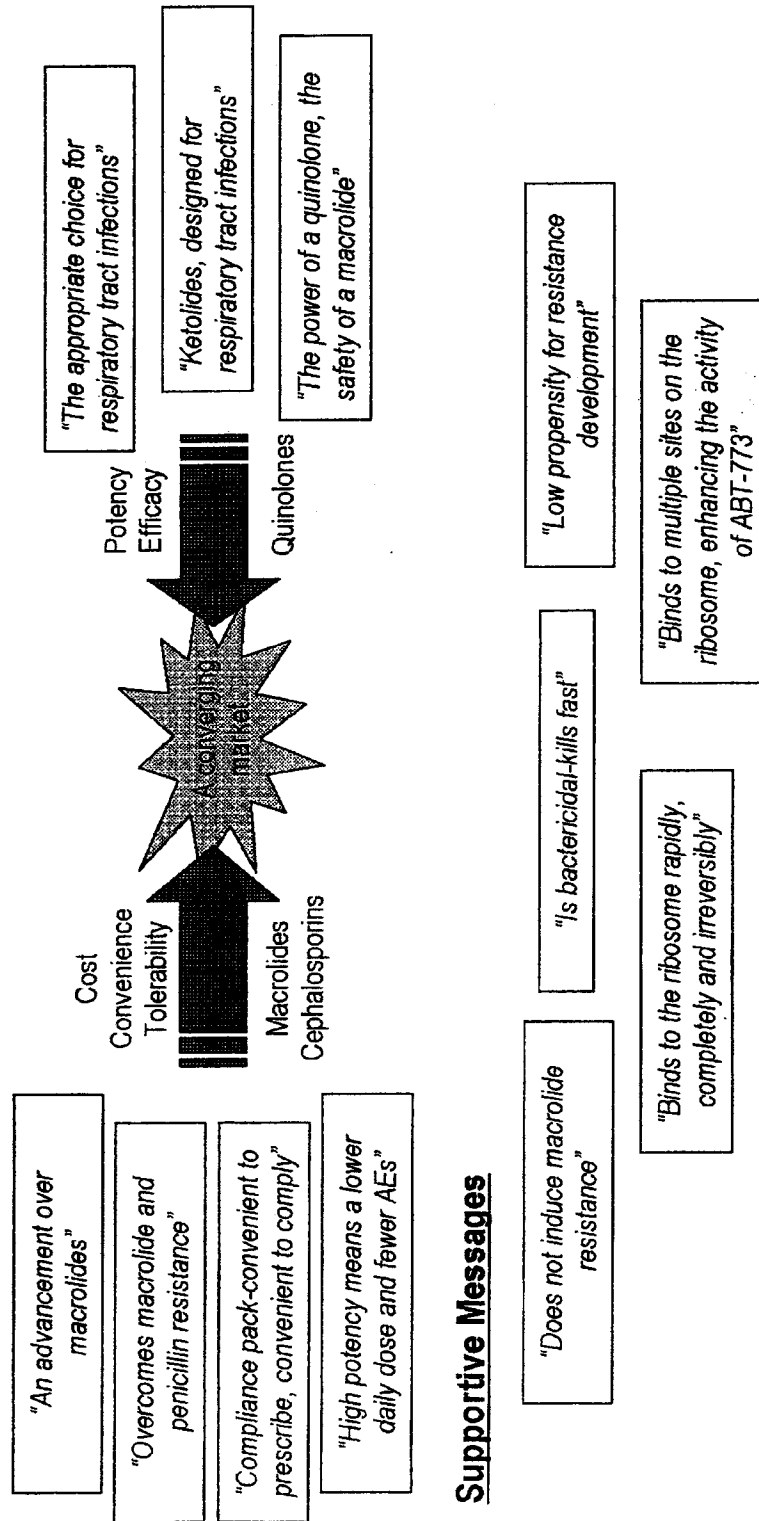
## PK Issue

Quinolones are using PK as means of differentiating products-could increase the relevance of PK to prescribers





## Key Commercial Messages



## Supportive Messages

## ***Communications Strategy***

- **Messages**
  - microbiological data (resistance, the better ketolide)
  - PK (no food effect, favorable drug-drug)
  - Mechanism (ribosome binding, PAE, etc., “explanation” for ketolide activity, defense of dose selection
  - Clinical data
- **Implementation**
  - Strategic initiation of studies to support desired messages, monthly strategy meetings, intranet under development to manage activities/history
  - Scientific meetings (51 posters at 6 scientific meetings in 1999-2000)
  - Publications (10 publications in 2000)
  - Medical Liaisons(sp)
  - VIP Visits

## **ICAAC 2000**

*International Conference on Antimicrobial Agents and Chemotherapy, Toronto*



**See you at ICAAC 2001, in Chicago,  
Illinois!!**

***Forecast Assumptions***

	<u>US</u>	<u>Europe</u>	<u>Japan</u>
Dosing	150 mg QD dosing all indications AECB & Phar, 5 d CAP & ABS, 10 d		
Efficacy	Comparable to other agents		
AEs	Comparable to Biaxin XL		
COGS	\$3,000/kg at launch		
AWP/Day	\$8.60		

**Forecast**

	<u>U.S.</u>	<u>Europe</u>	<u>Japan</u>	<u>ROW</u>	<u>Total</u>
Peak Sales	\$432MM				
Peak TRX Share	7.5%				N/A
NPV @12.5%					

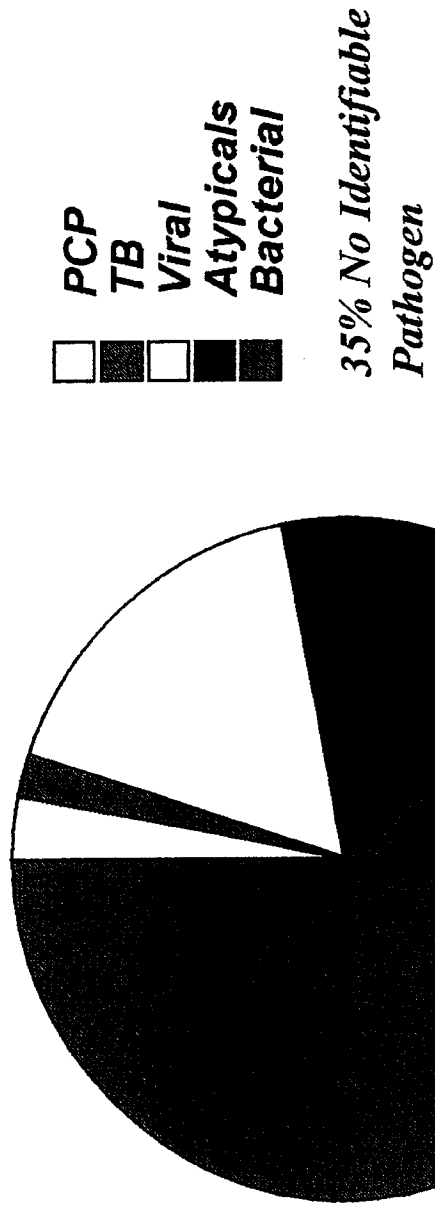
## **Microbiology**

### **Overview**

- **Ketolides are a Novel Class of Antimicrobial**
  - Active vs. key respiratory tract infection pathogens to include macrolide resistant streptococci
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development



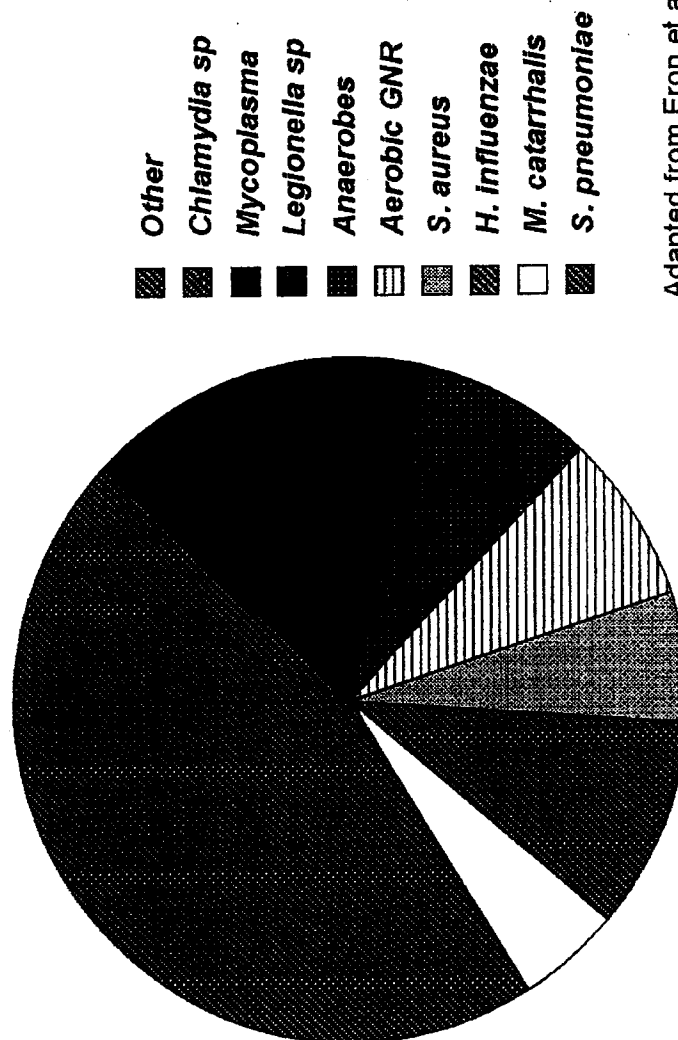
**Microbiology**  
**Community-Acquired Pneumonia in Adults**



Adapted from Eron et al. Hosp Form 1994;29:122

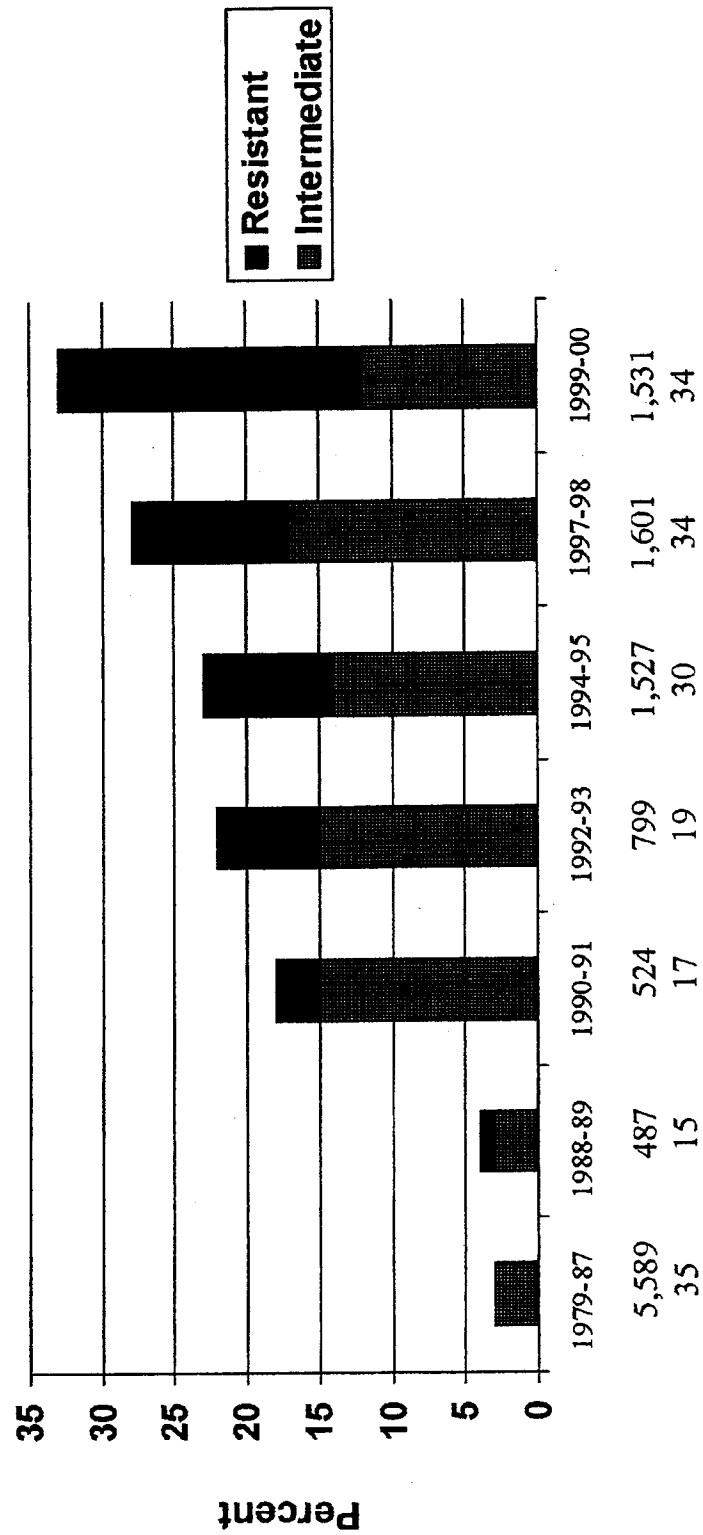
## **Microbiology**

### **Bacterial Causes of Community-Acquired Pneumonia in Adults**



Adapted from Eron et al. Hosp Form 1994;29:122

**Microbiology**  
*Penicillin resistance with Streptococcus pneumoniae in the United States*



## Microbiology

### *US Respiratory Surveillance Studies, Penicillin Susceptibility in S. pneumoniae*

Year	1994-95	1997-98	1999/2000
Season	Winter	Winter	Winter
No. of centers	30	34	34
No. of isolates	1,528	1,601	1,531
No. % intermediate	216 (14.1)	278 (17.4)	194 (12.7%)
No. % resistant	145 (9.6)	196 (12.2)	29 (21.5%)

Dr. G. Doern, Univ. of Iowa

**Microbiology**  
**Antimicrobial Resistance Rates among S. pneumoniae**

		1994-96	1997-98	1999-2000
Antimicrobial Agent		N=1527	N=1601	N=1531
Macrolide		10.0	18.9	25.9
Tetracycline		7.5	12.9	16.4
Chloramphenicol		4.3	7.2	8.4
Clindamycin		Na	5.6	8.8
TMP/SMX		18.0	20.4	30.3

Dr. G. Doern, Univ. of Iowa

**Microbiology**  
***Rates of Resistance of Non-  $\beta$ -Lactam Antimicrobials with Streptococcus pneumoniae  
Based on Penicillin Susceptibility Category***

**Percentage Resistance Among**

<u>Antimicrobial</u>	<u>PenS-(n=1,008)</u>	<u>PenI(n=194)</u>	<u>PenR(n=1,531)</u>
Macrolides	5.6	43.3	78.1
Clindamycin	1.4	19.1	25.2
Chloramphenicol	1.0	13.9	27.7
Tetracycline	3.1	32.0	48.0
TMP/SMX	7.6	39.2	94.5

[n=1,531, 34 U.S. centers, 1999-2000], Doern et al

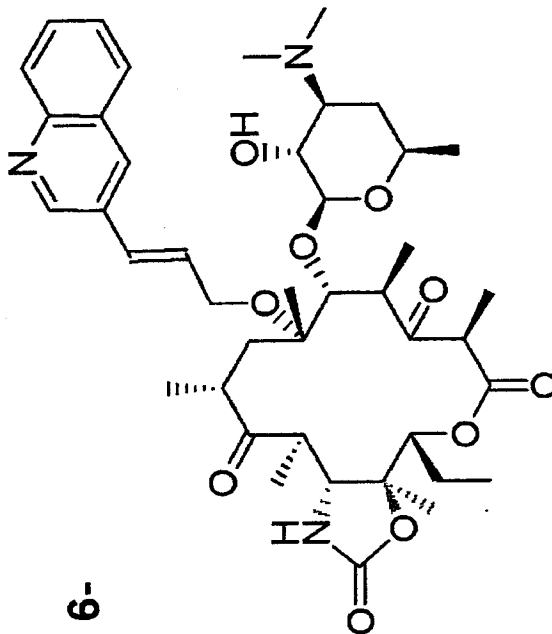


**Microbiology**  
**ABT-773 Structure/SAR**

•Quinolylallyl propenyl moiety at the 6-  
0 -position

•Keto group at the 3-position

•Carbamate group at the  
11, 12-position



**ABT-773**

## **Microbiology**

### **Macrolide Resistance Types**

#### **Microbiology Overview**

- Two major macrolide resistance mechanisms in streptococci and staphylococci:
  - Ribosomal methylase – blocks macrolide binding to target
    - Macrolide and clindamycin MIC >16 µg/mL
  - Macrolide efflux – actively pumps macrolide out of cell
    - Macrolide MIC 1-32 µg/mL; clindamycin MIC ≤ 0.25 µg/mL

**Microbiology**  
**Resistance Mechanisms Prevalence in *S. pneumoniae* Clinical Isolates**

Genotype	U.S. 1994-95 <sup>1</sup> n=114	U.S. 1997-98 <sup>2</sup> n=302	Canada <sup>3</sup> n=147	Europe <sup>4</sup> n=21	Japan <sup>5</sup> n=62
<i>ermB</i>	32%	29%	39%	97%	40%
<i>mefE</i>	61%	71%	56%	3%	43%
<i>mef/erm</i>	5%	-	<1%	-	16%
Unknown	2%	-	6%	-	0%

<sup>1</sup>Shortridge, et al. *C/D*. 1999; 29:1186-8.

<sup>2</sup>Doern, et al. *E/D*. 1999; 5(6).

<sup>3</sup>Johnston, et al. *AAC*. 1998; 42:2425-26.

<sup>4</sup>Schmitz et. al. *JAC*. 1999.43:783-92

<sup>5</sup>Nishijima et. al. *JAC*. 1999.43:637-643

**Microbiology**  
**ABT-773 Activity, University of Iowa Resistance Survey**

**Isolates by Erythromycin MIC**

Drug	Erythromycin MIC $\leq 0.5 \mu\text{g/ml}$ (n=1299)		Erythromycin MIC 1-32 $\mu\text{g/ml}$ (n=222)		Erythromycin MIC $\geq 64 \mu\text{g/ml}$ (n=80)	
	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	$\leq 0.008$	$\leq 0.008 - 0.12$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.5$

1997-1998 Survey, Brueggemann et. al.2000. AAC. 44:447-449

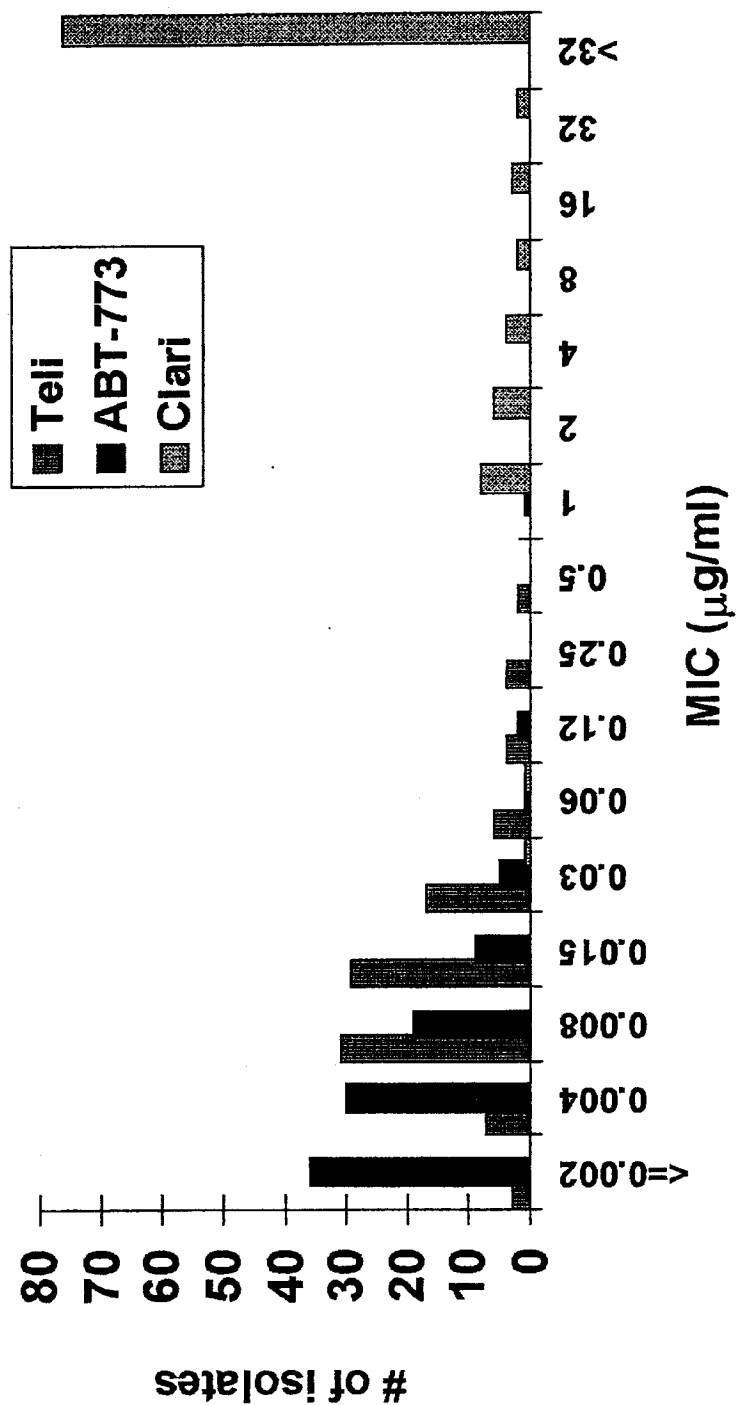
**Microbiology**  
**ABT-773 Activity, University of Iowa Resistance Survey**

**Isolates by Penicillin MIC**

	Penicillin Susceptible MIC $\leq 0.06$ $\mu\text{g/ml}$ (n=1127)		Penicillin Intermediate MIC 0.12-1.0 $\mu\text{g/ml}$ (n=278)		Penicillin Resistant MIC $\geq 2.0$ $\mu\text{g/ml}$ (n=196)	
	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
<b>ABT-773</b>	$\leq 0.008$	$\leq 0.008 - 0.5$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.25$
<b>Ery</b>	0.06	$\leq 0.03 - >64$	>64	$\leq 0.03 - >64$	>64	$\leq 0.03 - >64$

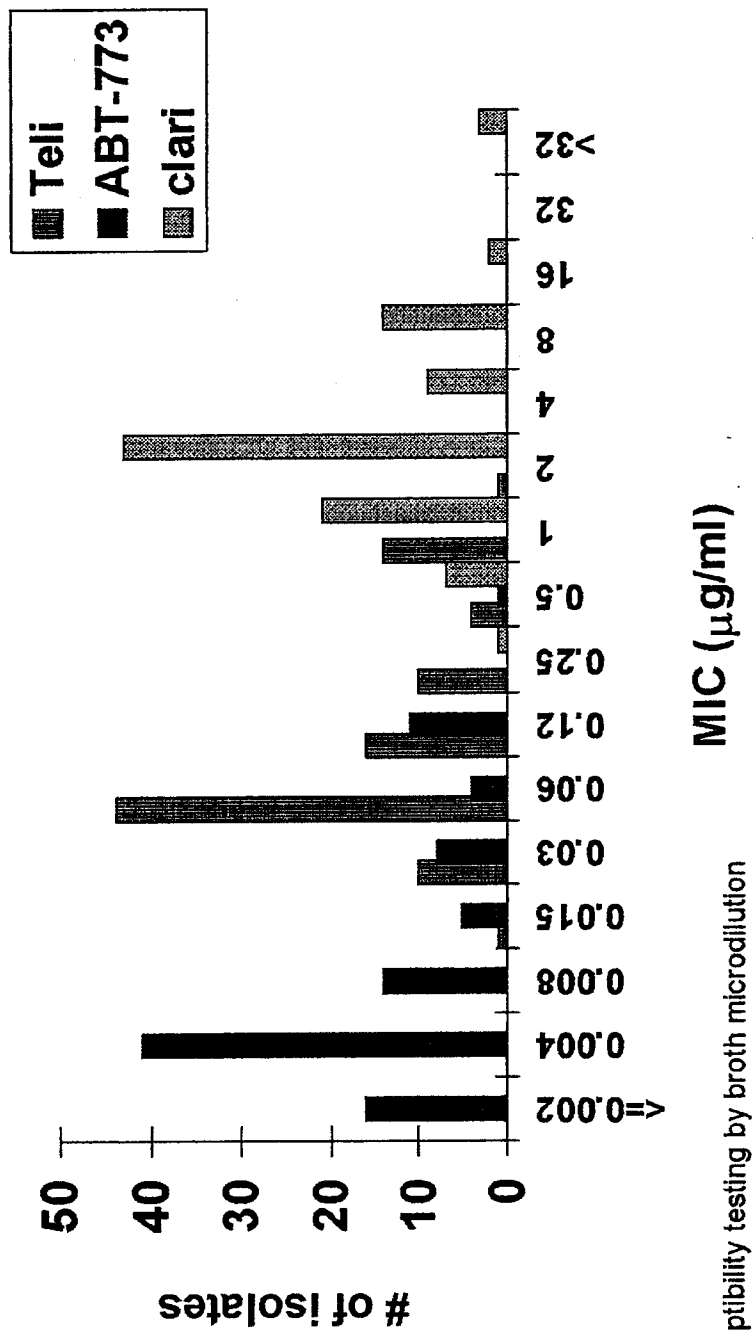
1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449

**Microbiology**  
**MIC Distribution of *S. pneumoniae* methylase<sup>+</sup> strains**





**Microbiology**  
*MIC Distribution of S. pneumoniae efflux<sup>+</sup> strains*



**Microbiology**  
*In vitro* Activity, *S. pyogenes*

MIC<sub>90</sub> Range in µg/ml

Organism	Macrolide susceptible	Macrolide resistant
ABT-773	≤0.016 - 0.03	0.06 - 0.12
Erythromycin	0.06 - 0.12	8 - 16

References:

Barry et al ICAAC 1999 #2144  
Dubois et al. ICMASKO 2000 #2.15  
Singh et al. ICMASKO 2000 #2.14

**Microbiology**  
*In vitro Activity , Haemophilus, Moraxella spp.*

MIC<sub>90</sub> Range in µg/ml

Organism	<i>H. influenzae</i>	<i>M. catarrhalis</i>
ABT-773	2 - 4	0.06 – 0.25
Azithromycin	2 - 4	0.06 - 0.12
Erythromycin	8 - 16	0.25 - 0.5

References:

Barry et al ICAAC 1999 #2144  
 Hoellman et al ICAAC 1999 #2140  
 Brueggemann et al. 2000.AAC.44:447-449  
 Shortridge et. al.1999. ICAAC

**Microbiology**  
**Comparison of activity vs. respiratory atypical pathogens**

MIC<sub>90</sub> in µg/ml

Organism	ABT-773	Ery
<i>Legionella</i> spp. <sup>1</sup> (105)	0.03-0.12	0.25-1.0
<i>M. pneumoniae</i> <sup>2</sup> (18)	≤ 0.0005	0.008
<i>C. pneumoniae</i> <sup>3</sup> (20)	0.015	0.06

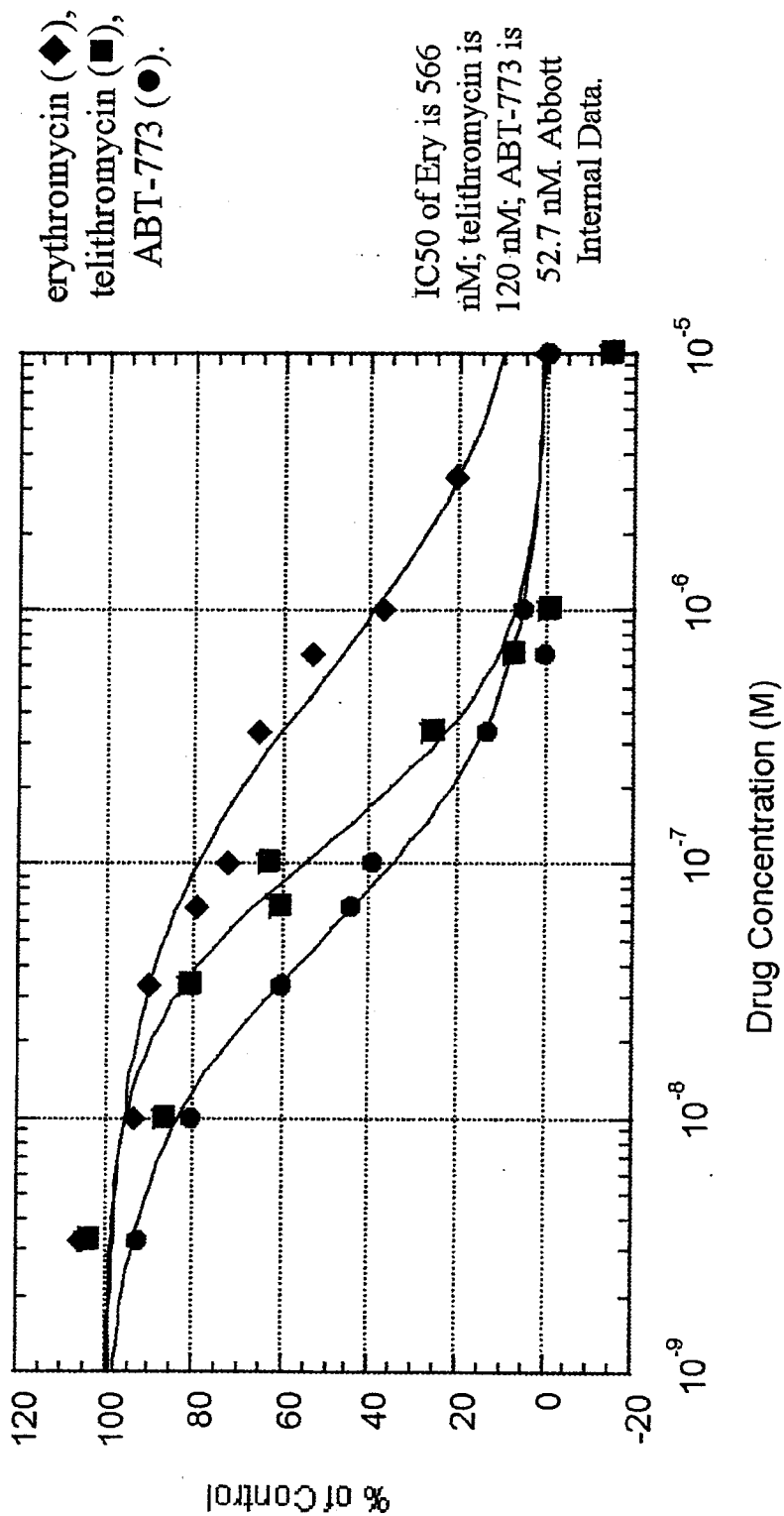
<sup>1</sup>Victor Yu, ICAAC, 2000. Strains tested: *L. pneumophila* serogroup 1 (68), *L. pneumophila* other serogroups (28), *Legionella* spp other than pneumophila (10).

<sup>2</sup> Nilius et al. ECCMID 1999.

<sup>3</sup> Strigl et. al.2000. AAC.44:1112-1113

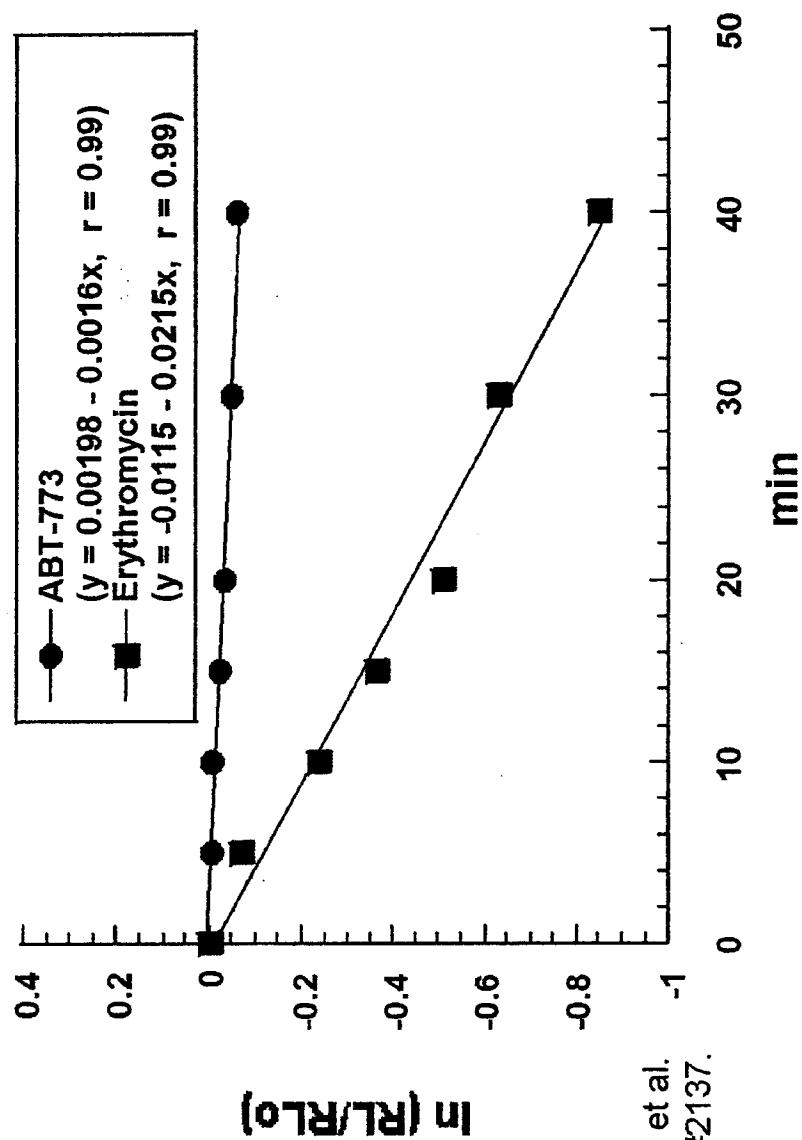


**Microbiology**  
**Ribosome Binding, Susceptible *S. pneumoniae***





# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486

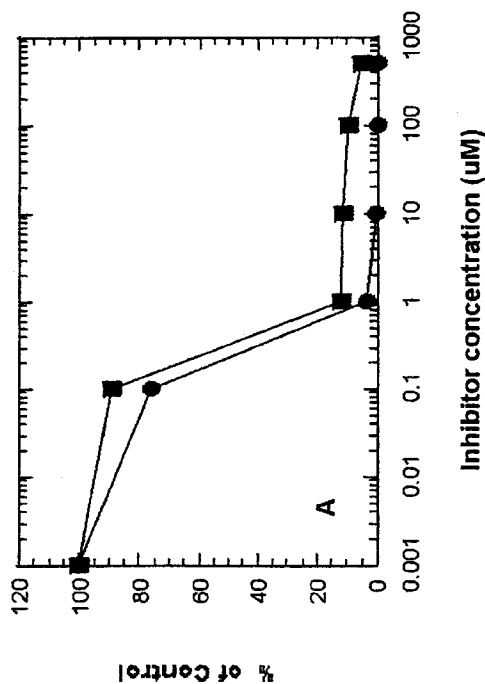


J. Capobianco et al.  
 ICAAC 1999, #2137.

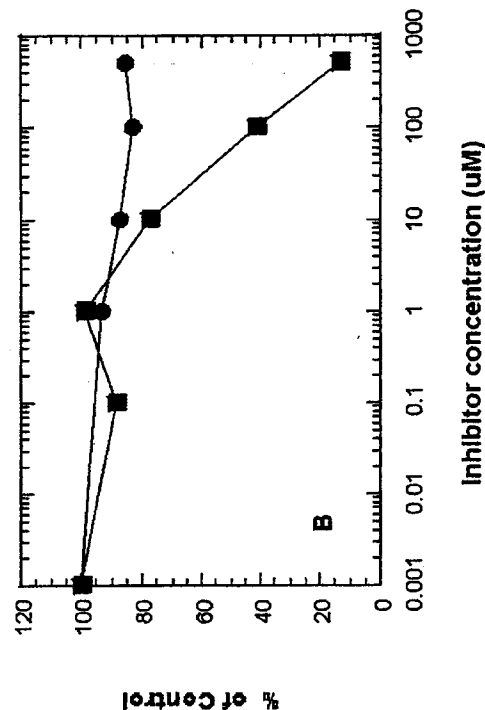
# Microbiology

## Inhibition of Transcription / Translation

S30 from susceptible *S. pneumoniae*



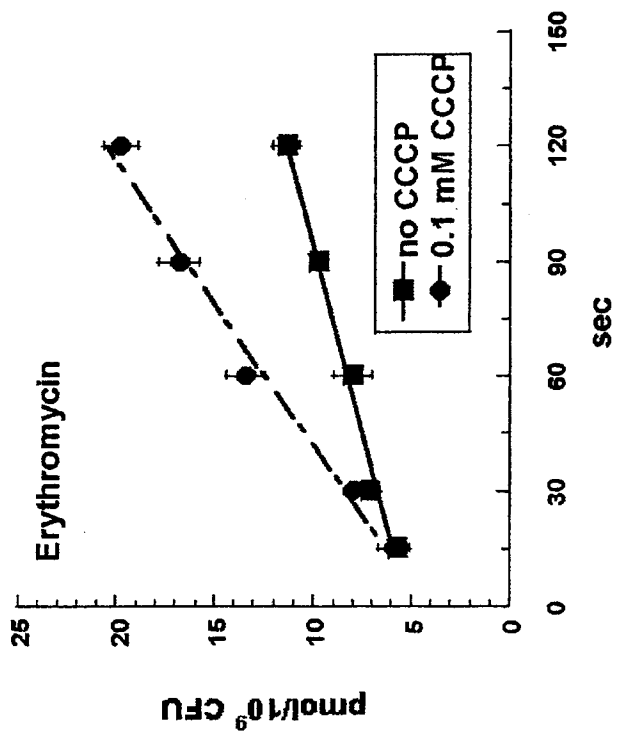
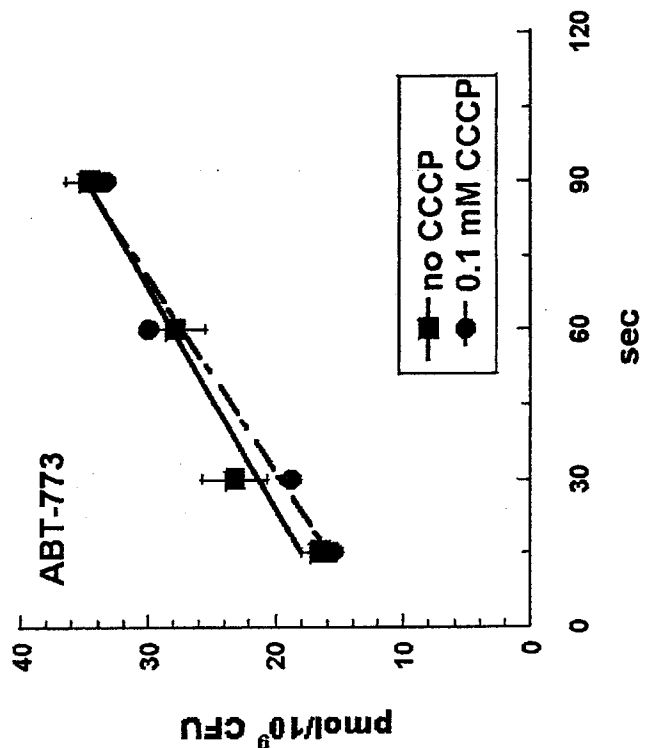
S30 from resistant *S. pneumoniae*



Red circles: erythromycin  
Blue squares: ABT-773

Z Cao et. al. ICAAC 1999. Poster #2135.

# **Microbiology** **ABT-773 Accumulation in efflux<sup>+</sup> strain, with and without pump inhibitor (CCCP)**

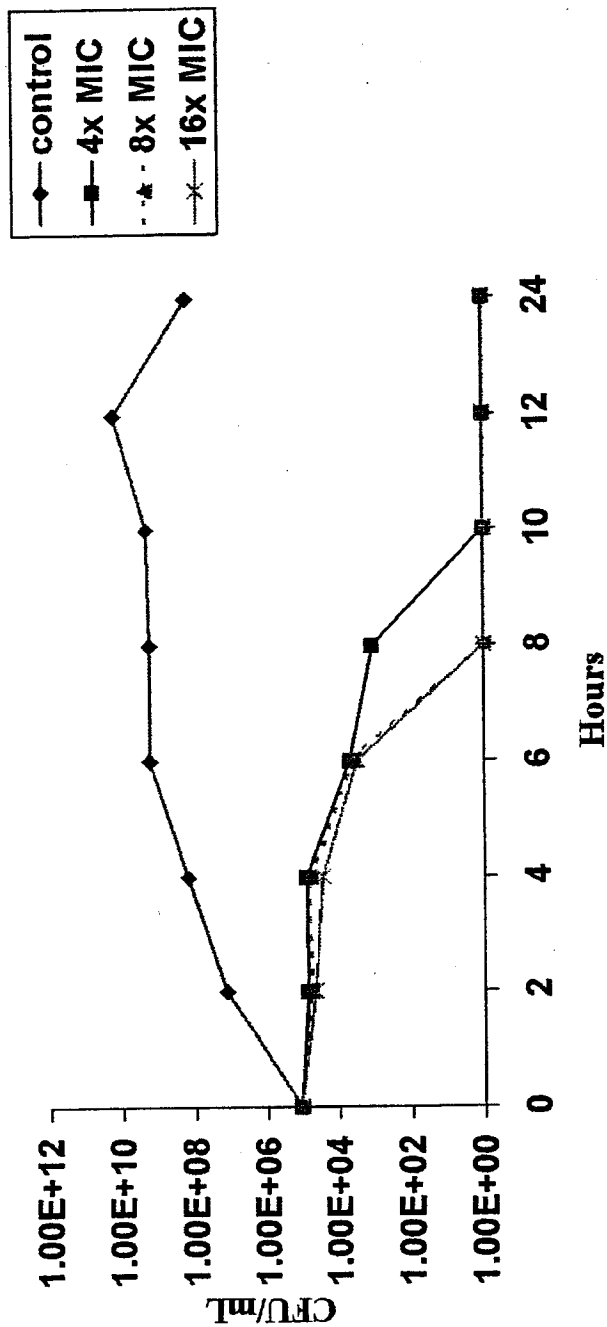


J. Capobianco et al. ICAAC 1999, #2137

## Microbiology

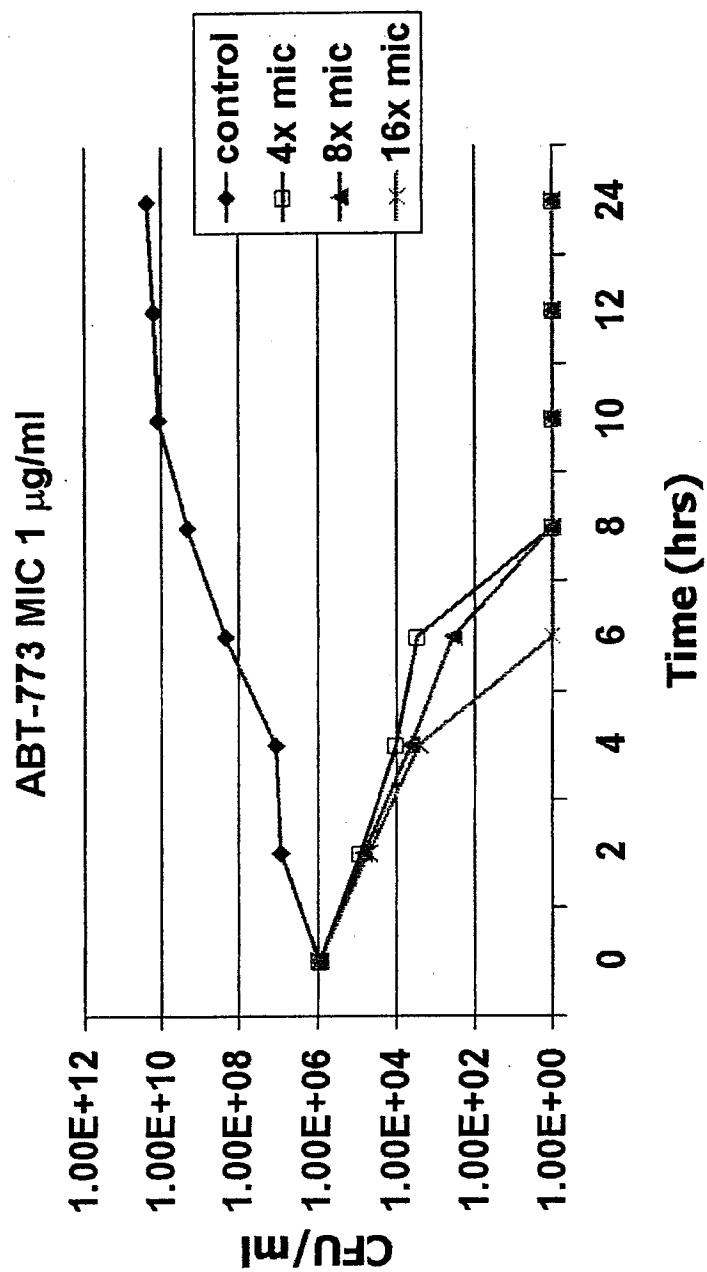
### Bactericidal Activity, *S. pneumoniae*

Susceptible *S. pneumoniae*; ABT-773 MIC 0.002 µg/ml



Ramer et al. ICAAC 2000

**Microbiology**  
**Bactericidal Activity, *H. influenzae***



## **Microbiology**

### **Post Antibiotic Effect**

- After removal of drug the bacterial growth rate is inhibited
- Justification for dosing regimen such as QD vs. BID
- Addresses resistance development issues
- In vitro
  - *S. pneumoniae*
    - 8 strains
    - mean PAE ABT-773  $\geq 6.1$  hr
    - mean PAE ery 3.8hr
  - *H. influenzae*
    - 5 strains
    - mean PAE ABT-773  $\geq 6.1$  hr
    - mean ery PAE 3.8 hr

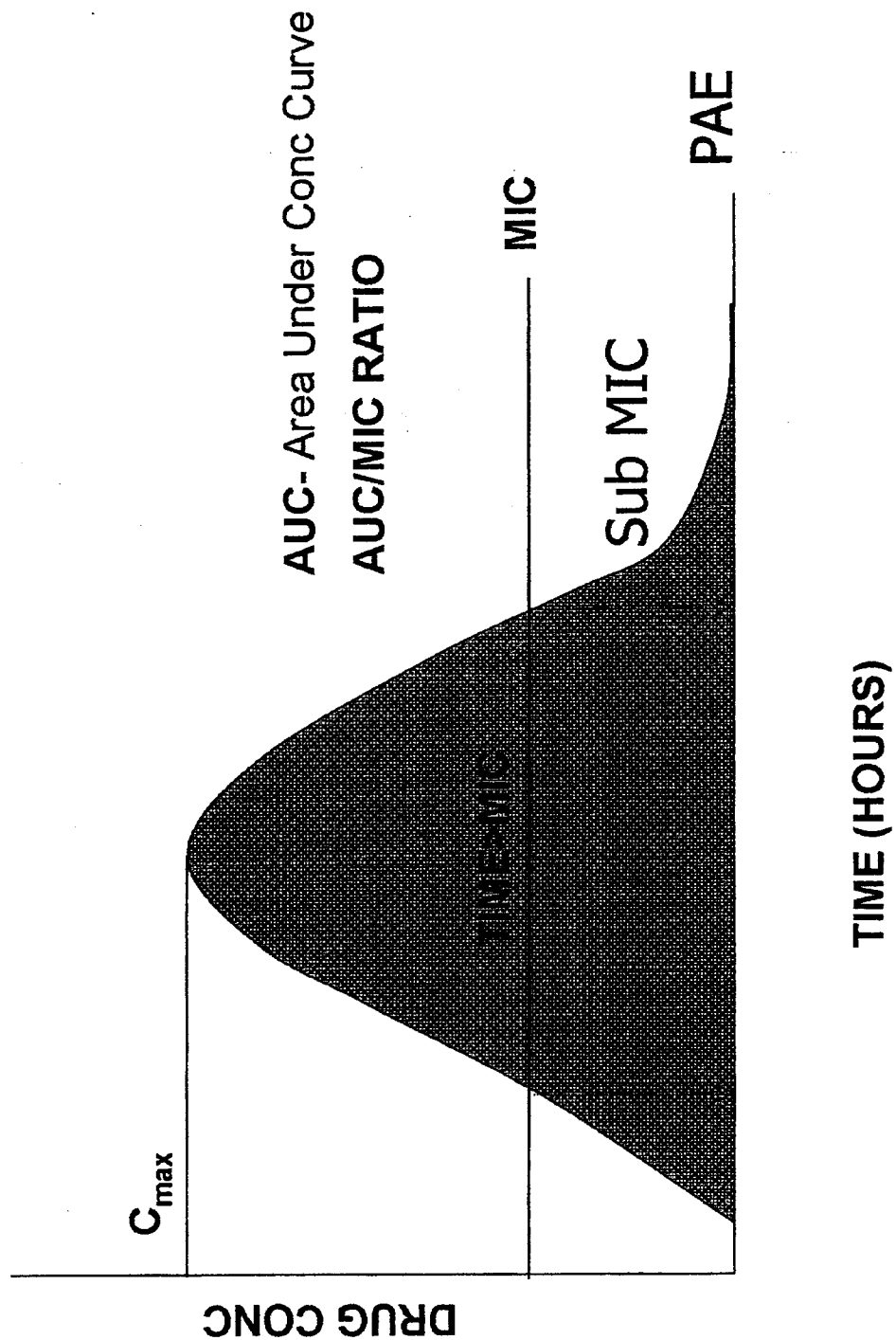


## **Microbiology**

### **Resistance Development**

- **Occur by mutation**
  - Quinolone resistance in GyrA and ParC
- **Acquired from another bacterium**
  - Methylase
  - Efflux
- ***S. pneumoniae***
  - In vitro single step mutation frequency (8XMIC)
    - 1 *S. pneumoniae* (S)  $<5.6 \times 10^{-10}$
    - 1 *S. pneumoniae* *mef*  $<2.6 \times 10^{-12}$
    - 2 *S. pneumoniae* *ermB*  $3.5 \times 10^{-10}$ – $9.4 \times 10^{-11}$
  - Mutation frequency for rifampicin (8XMIC)
    - 4 *S. pneumoniae*  $1.2 \times 10^{-6}$  to  $3.0 \times 10^{-7}$
  - No difference in mutation rate if macrolide resistant or susceptible
  - Low potential for resistance development

**Microbiology**  
Pharmacodynamic Parameters



**Microbiology**  
*In vivo pharmacodynamics*

- Antibiotic exposure needed for efficacy against *S. pneumoniae* in animal models
  - AUC/MIC is best predictive parameter for ketolides
  - Rat lung model of pneumonia with *S. pneumoniae*
    - QD an AUC 0-24 ug.h/ml of 0.4-1.0 for an MIC<sub>90</sub> of 0.12
    - BID an AUC 0-24 ug.h/ml of 0.1-0.4 for an MIC<sub>90</sub> of 0.12
  - Lethal mouse model of pneumonia AUC 0-24 of <3-6 ug.h/ml

**Microbiology**  
*In vivo pharmacodynamics*

- Neutropenic mouse thigh model
  - *S. pneumoniae*
    - 6 macrolide susceptible , 8 macrolide resistant
    - $10^{5.8-7.4}$  CFU/ thigh
    - ABT-773 dose 0.023-24 mg/kg/day Q6 h
    - Net bacteriostatic effect over 24 hrs is measured

Andes, D.R. and W.A. Craig. ICAAC 2000.

**Microbiology**  
*In vivo pharmacodynamics*

- **Neutropenic mouse thigh model- *S. pneumoniae***
  - 24hr AUC/MIC is best PK/PD predictor
  - Prolonged PAEs with concentration dependent killing
    - up to 11 hrs
  - Magnitude of AUC/MIC is not significantly altered by macrolide resistance with strains with MICs as high as 0.5µg/ml

Andes, D.R. and W.A. Craig. ICAAC 2000

## **Microbiology**

### ***In vivo pharmacodynamics***

- **Mouse lethal pneumonia model**

- *S. pneumoniae*-2 strains
  - eryS
  - eryR
- immunocompetent mice
- infected with  $10^{4-5}$  CFU
- treatment 6 or 12 hr post-infection
- subcutaneous dosing
- BID treatment for 3 days

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.

**Microbiology**  
*In vivo pharmacodynamics*

- **vs. macrolide susceptible**
  - Ery/ABT-773 MIC 0.015/0.015 ug/ml
    - 100% survival with 3 days of treatment at s.c. 6.25mg/kg
- **vs. macrolide resistant**
  - Ery/ABT-773 MIC 1024/0.03 ug/ml
    - 93% survival with 3 days of treatment s.c. at 12.5 mg/kg
      - » infected mouse single dose 12.5 mg/kg- AUC 0-24 ug.h/ml  
3.08+/- 0.32)

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Rlex, Mohler, Carbon et. al. ICAAC 2000.



**Microbiology**  
*In vivo pharmacodynamics*

- Suggests total daily AUC 0-24 ug.h/ml of  $<3-6$  is sufficient for pneumonia
  - ketolide is active vs macrolide resistant strain unlike erythromycin
  - no resistant mutants emerged vs ABT-773 but did for erythromycin

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.

## **Microbiology**

### **Summary**

- Active vs. key respiratory pathogens including macrolide resistant streptococci
- Bactericidal
- Extended PAE
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome
  - Exposure of  $<1 \text{ ug.h/ml AUC}_{24}$  for mild to moderate pneumonia model and  $\text{AUC}_{24} \text{ ug.h/ml} <3\text{-}6$  for more severe model

**Phase II Clinicals**  
**Joaquin Valdes**

## Phase II Clinicals

### Program Summary

Study	Study Drug Dose/Duration	Patient Numbers/location
M99-048 Phase IIb, Double blind Acute Bacterial Exacerbation of Chronic Bronchitis	ABT-773 150, 300 or 600 mg OD Duration: 5 days	N = 384 US, Germany, France, Italy, Spain, UK, Chile
M99-053 Phase IIb, Double-blind Acute Sinusitis	ABT-773 150, 300, or 600 mg OD Duration: 10 days	N = 292 US, Finland, Greece, Chile
M99-054 Phase IIb, Double-blind Community Acquired Pneumonia	ABT-773 300 or 600 mg OD Duration: 7 days	N = 187 US, Germany, France, Italy, Spain, Poland, South Africa

**Acute Bacterial Exacerbation of Chronic Bronchitis**  
**M99-048**  
**Clinical Response**

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	88% (49/56)	94% (59/63)
Clin Eval	87% (98/113)	90% (105/117)	90% (101/112)
ITT	85% (104/123)	83% (107/129)	83% (106/128)

**Acute Bacterial Exacerbation of Chronic Bronchitis**  
**M99-048**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	83% (10/12)	90% (9/10)	100% (13/13)
<i>M. catarrhalis</i>	80% (8/10)	92% (12/13)	91% (10/11)
<i>H. influenzae</i>	94% (17/18)	89% (17/19)	83% (19/23)
Overall	88% (35/40)	91% (38/42)	89% (42/47)

**Acute Bacterial Exacerbations of Chronic Bronchitis**  
**M99-048**  
**Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
<b>Taste Perversion</b>	6% (7/126)	19% (25/129)	29% (37/129)
<b>Diarrhea</b>	13% (16/126)	12% (15/129)	21% (27/129)
<b>Nausea</b>	7% (9/126)	13% (17/129)	30% (38/129)
<b>Vomiting</b>	2% (3/126)	3% (4/129)	11% (14/129)
<b>Nausea and Vomiting</b>	0	<1% (1/129)	4% (5/129)
<b>Abdominal Pain</b>	4% (5/126)	4% (5/129)	4% (5/129)



**Community-Acquired Pneumonia  
M99-054  
Clinical Response**

300 mg                      600 mg

Clin and Bact. Eval	92% (54/59)	82% (47/57)
Clin Eval	92% (72/78)	80% (56/70)
ITT	84% (80/95)	73% (65/89)

**Community-Acquired Pneumonia  
M99-054  
Radiographic Response**

**(Resolution/Improvement)**

	300 mg	600 mg
Clin and Bact. Eval	100% (56/56)	89% (48/54)
Clin Eval	99% (73/74)	88% (57/65)
ITT	84% (80/95)	72% (64/89)

**Community-Acquired Pneumonia  
M99-054  
Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	300 mg		600 mg
<i>S. pneumoniae</i>	87%	(13/15)	100% (7/7)
<i>M. catarrhalis</i>	75%	(6/8)	50% (2/4)
<i>H. influenzae</i>	100%	(9/9)	72% (13/18)
<i>M. pneumoniae</i>	93%	(13/14)	93% (14/15)
<i>C. pneumoniae</i>	95%	19/20)	79% (19/24)
<i>L. pneumoniae</i>	100%	(3/3)	100% (2/2)
Overall	91%	(63/69)	81% (57/70)

**Community-Acquired Pneumonia  
M99-054  
Adverse Events**

**All Adverse Events**

**300mg                      600mg**

**GI and Taste**

**Taste Perversion**

**17%                      (16/95)                      26%                      (24/92)**

**Diarrhea**

**14%                      (13/95)                      19%                      (17/92)**

**Nausea**

**12%                      (11/95)                      22%                      (20/92)**

**Vomiting**

**10%                      (9/95)                      15%                      (14/92)**

**Sinusitis  
M99-053  
Clinical Response**

	150 mg	300 mg	600 mg
Clin Eval	89% (70/79)	83% (70/84)	71% (59/83)
ITT	82% (72/88)	80% (72/90)	67% (59/88)

**Sinusitis  
M99-053  
Radiographic Response**

**(Resolution/Improvement)**

150 mg      300 mg      600 mg

Clin Eval

86% (68/79)      86% (71/83)      78% (59/76)

ITT

81% (71/88)      81% (73/90)      67% (59/88)

**Sinusitis**  
**M99-053**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	3/3	8/8	9/12
<i>M. catarrhalis</i>	8/9	3/4	4/4
<i>H. influenzae</i>	3/5	7/7	5/7
<i>S. aureus</i>	1/1	1/1	3/4



**Sinusitis  
M99-053  
Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	1% (1/97)	14% (14/98)	27% (26/97)
Diarrhea	6% (6/97)	6% (6/98)	17% (16/97)
Nausea	3% (3/97)	12% (12/98)	26% (25/97)
Vomiting	1% (1/97)	6% (6/98)	17% (16/97)

***Insert cure/erad/AE summary table***

**ABECB, CAP, AMS  
M99-048, M99-054, M99-053  
Clinical Response**

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

**ABECB, CAP, AMS  
M99-048, M99-054, M99-053  
Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	87% (13/15)	91% (30/33)	91% (29/32)
<i>M. catarrhalis</i>	84% (16/19)	84% (21/25)	84% (16/19)
<i>H. influenzae</i>	87% (20/23)	94% (33/35)	77% (37/48)
Overall	86% (49/57)	90% (84/93)	83% (82/99)

**ABECB, CAP, AMS  
M99-048, M99-054, M99-053  
Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	4% (8/223)	17% (55/322)	27% (87/318)
Diarrhea	10% (22/223)	11% (34/322)	19% (60/318)
Nausea	5% (12/223)	12% (40/322)	26% (83/318)
Vomiting	2% (4/223)	6% (19/322)	14% (44/318)

## ***Phase II summary***

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD will be evaluated in comparative studies of ABECB and pharyngitis in phase III
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

***Phase III Clinical Program  
Joaquin Valdes***



## Proposed Indications and Treatment Duration

Infection	Dosage (QD)	Duration (days)
Pharyngitis/Tonsillitis due to <i>S. pyogenes</i> *	150 mg	5
Acute bacterial sinusitis due to <i>H. influenzae</i>	150 mg (or BID)	10
<i>M. catarrhalis</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10
Acute bacterial exacerbation of chronic bronchitis due to <i>H. influenzae</i>	150 mg	5
<i>H. parainfluenzae</i>	150 mg	5
<i>M. catarrhalis</i>	150 mg	5
<i>S. pneumoniae</i> **	150 mg	5
Community-acquired pneumonia due to <i>C. pneumoniae</i>	150 mg (or BID)	10
<i>H. influenzae</i>	150 mg (or BID)	10
<i>L. pneumophila</i>	150 mg (or BID)	10
<i>M. pneumoniae</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10

\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.

**Phase 3 Studies****Studies starting in year 2000:**

<b>Study</b>	<b>Indication</b>	<b>ABT-773 Regimen</b>	<b>Comparator</b>	<b>Number ABT-773 Subjects</b>	<b>Location</b>
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	260	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	260	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	300	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	250	EU (Non-IND)

## Phase 3 Studies

**Studies starting in year 2000 (Cont.):**

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	600	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	800	US, Canada, EU (IND)

### ***Phase 3 Studies***

#### **Studies starting in year 2001:**

<b>Study</b>	<b>Indication</b>	<b>Comparator</b>	<b>Number ABT-773 Subjects</b>	<b>Location</b>
M00-221	CAP	Levofloxacin	225	US, Canada (IND)
M00-220	CAP	Augmentin or Amoxicillin	250	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	US, Canada (IND)
M00-218	Sinusitis	Augmentin or Quinolone	250	EU (Non-IND)

**Proposed Claim for Macrolide or  
Penicillin Resistant Bacteria and Atypicals**

<b>Claim</b>	<b>Supporting Data</b>
Macrolide-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Penicillin-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Macrolide-resistant <i>S. pyogenes</i>	15 isolates worldwide from Phase 3 pharyngitis
Atypicals; <i>C. pneumoniae</i> , <i>M. pneumoniae</i> , <i>Legionella spp.</i>	15 isolates worldwide per organism (include positive serology) from Phase 3 CAP

**Bulk Drug Manufacturing**  
**Ashok Bhatia**

# ***Bulk Drug Manufacturing***

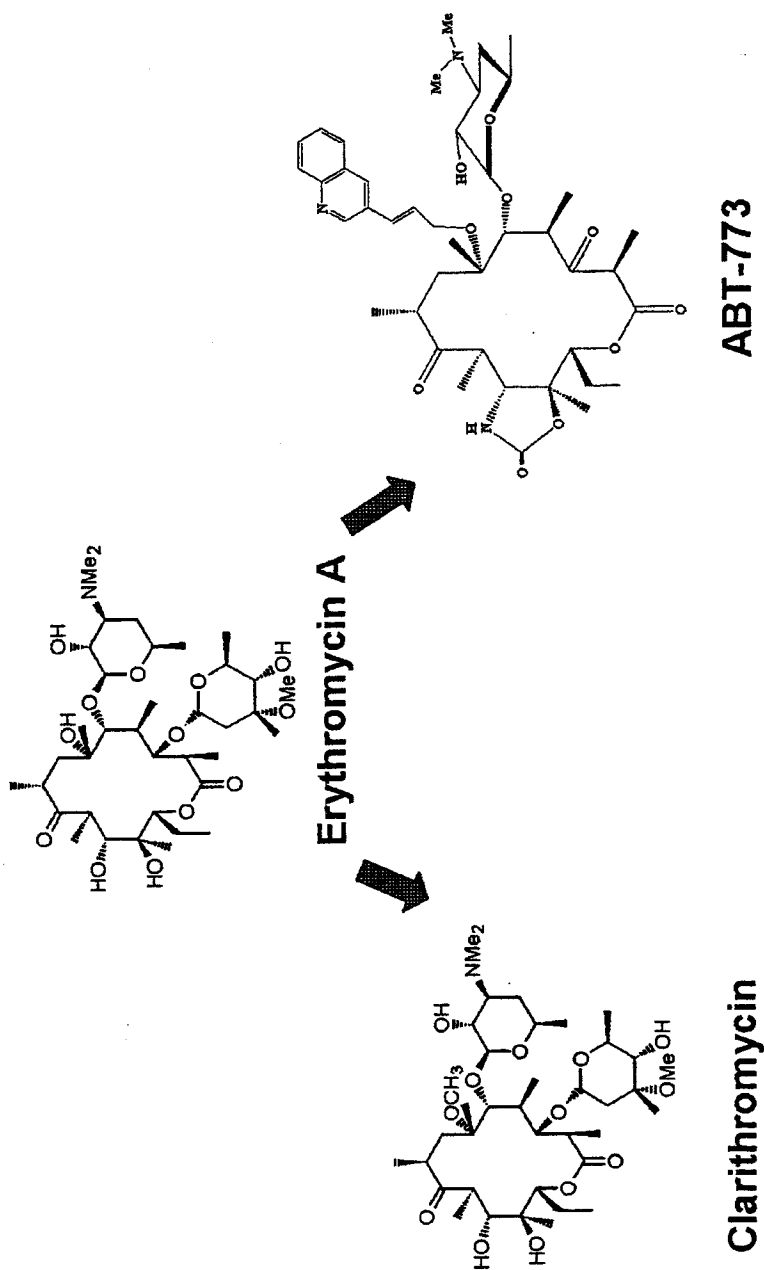
## **Agenda**

### **Agenda**

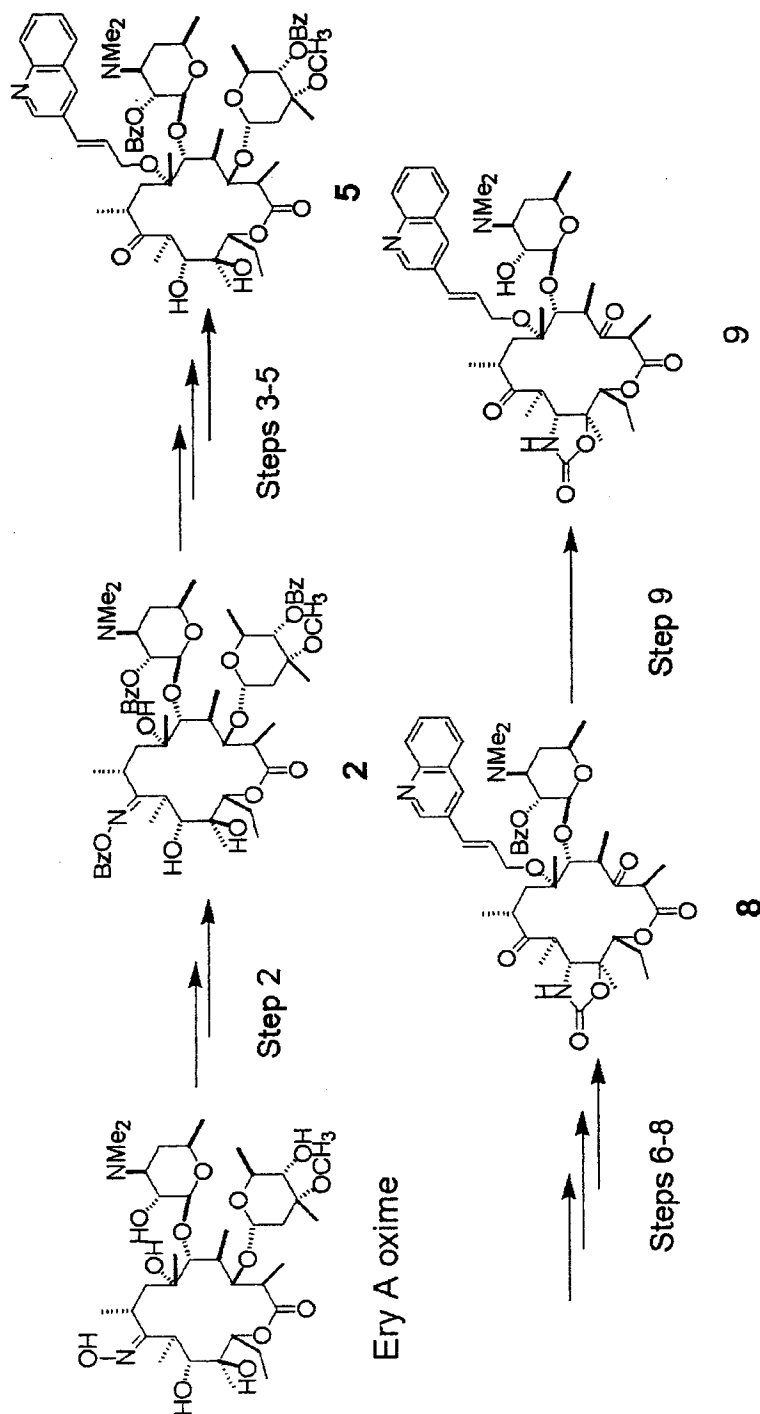
- **Chemistry**
- **Process Strategy and Review**
- **Cost Review and Projection**



**Bulk Drug Manufacturing**  
Macrolide Structures



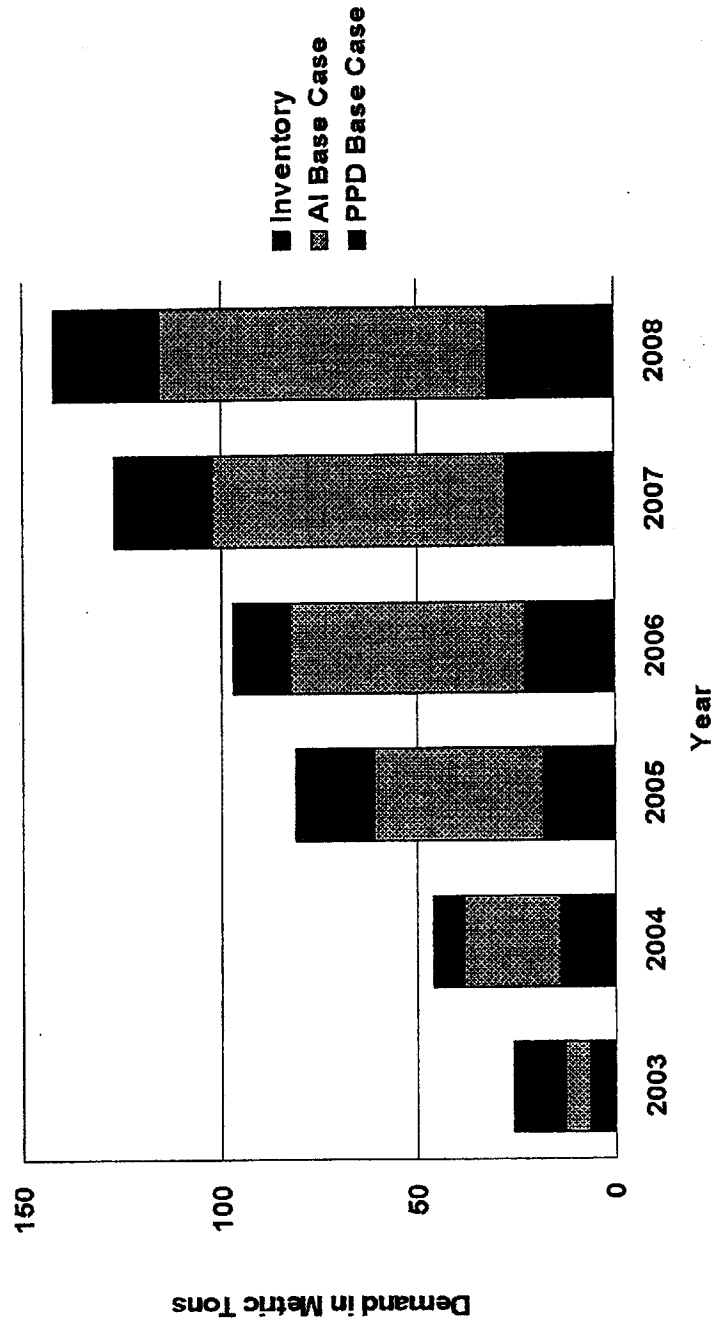
# **Bulk Drug Manufacturing** **ABT-773 Synthesis**



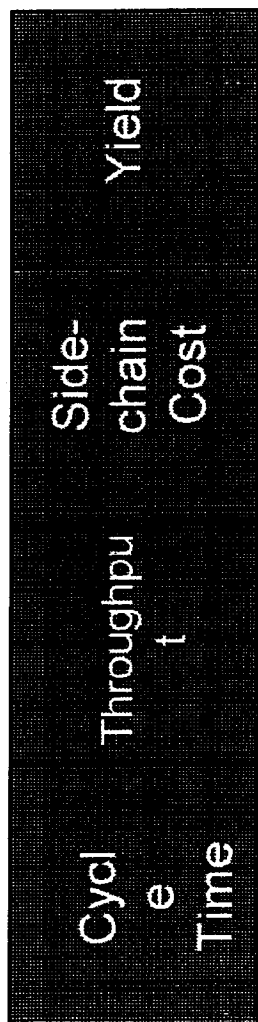
ABT - 773

**Bulk Drug Manufacturing**  
Drug Substance Demand

**ABT-773 Bulk Demand - Consolidated LRP**



# *Bulk Drug Manufacturing Process Improvements*



	1998	1999	2000
CycleTime (Days)	53	35	30
Throughput Batch Size Manuf. Sites	100 kg 1	175 kg 5	350 kg 5
Side-chain Cost	\$2500/kg	\$1100/kg	\$950/kg
Yield (%)	18	21	28

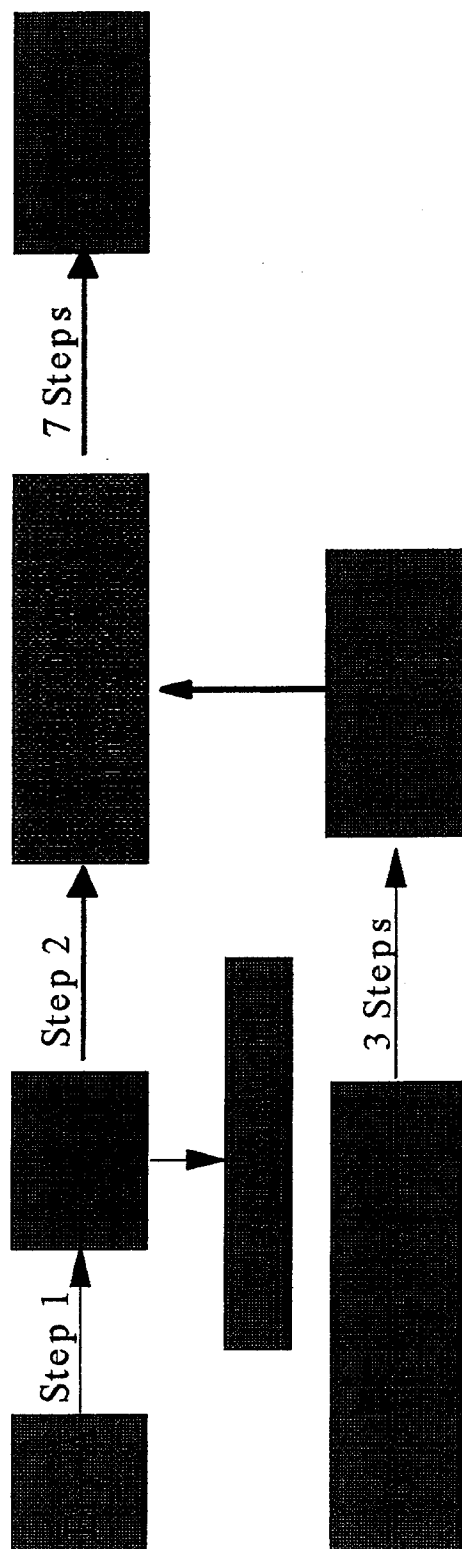
***Bulk Drug Manufacturing***  
*Comparison of Projected & Actual Demand/Cost*

	1999	2000	2001
Demand (kg)	1,400	2,520	1,675
Actual (kg)	1,488	2,815	
Projected (\$)	\$10,000	\$6,500	\$5,000
Actual (\$)	\$7,800	\$5,400 (est.)	

Bulk Drug

Cost/kg

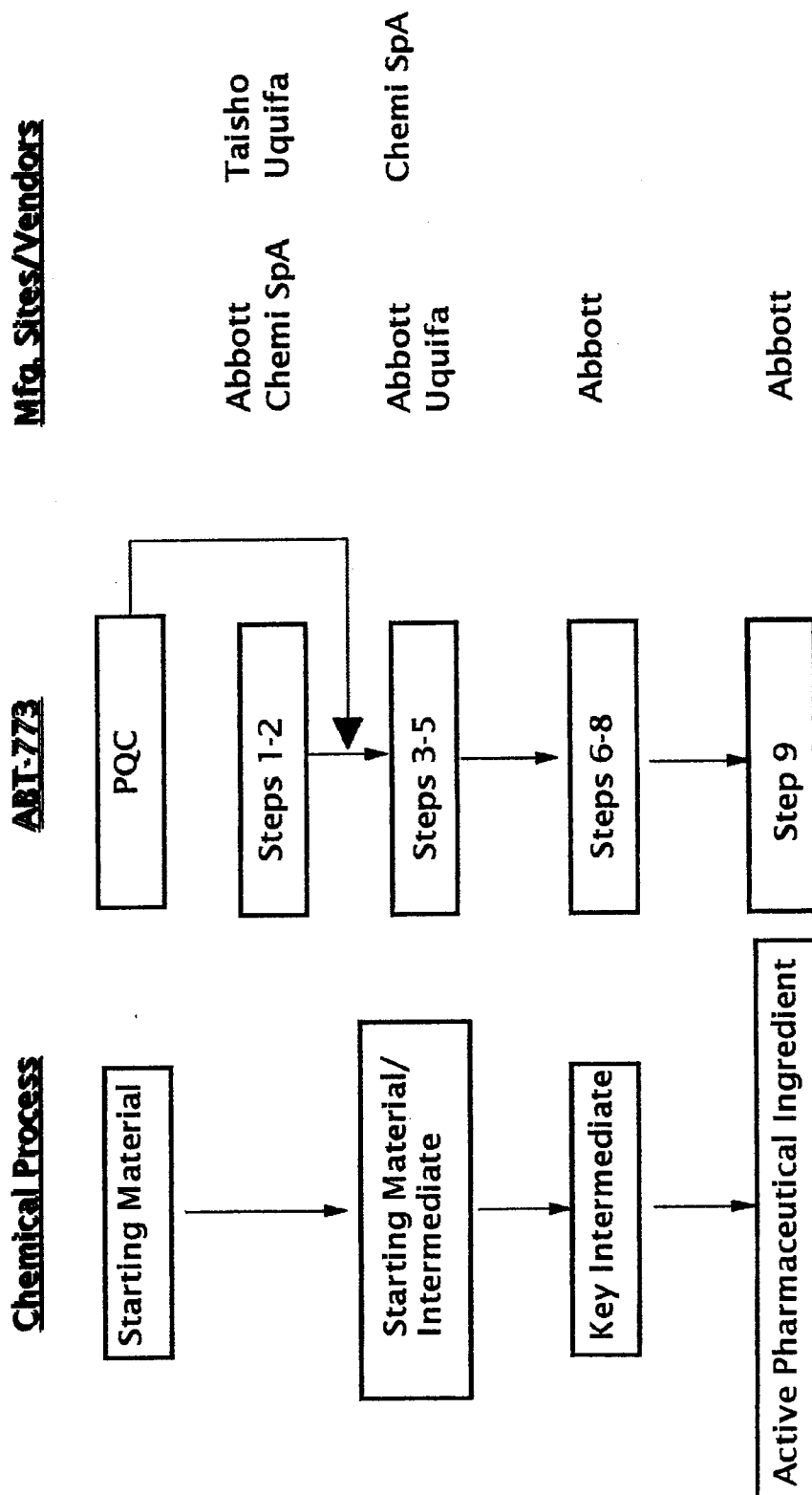
## **Bulk Drug Manufacturing** *Synthesis*



- Bromoquinoline sources from India and China
- Side-chain outsourced from India and Europe
- Intermediates up to Step 5 outsourced/internal

# Bulk Drug Manufacturing

*Manufacturing Strategy: Starting Materials & Intermediates*





***Bulk Drug Manufacturing***  
***Step 5 as Starting Material***

**Criteria:**

Readily available at commercial scale  
Structure incorporated in Drug Substance molecule  
Well-characterized and known impurity profile  
Prepared by know methods

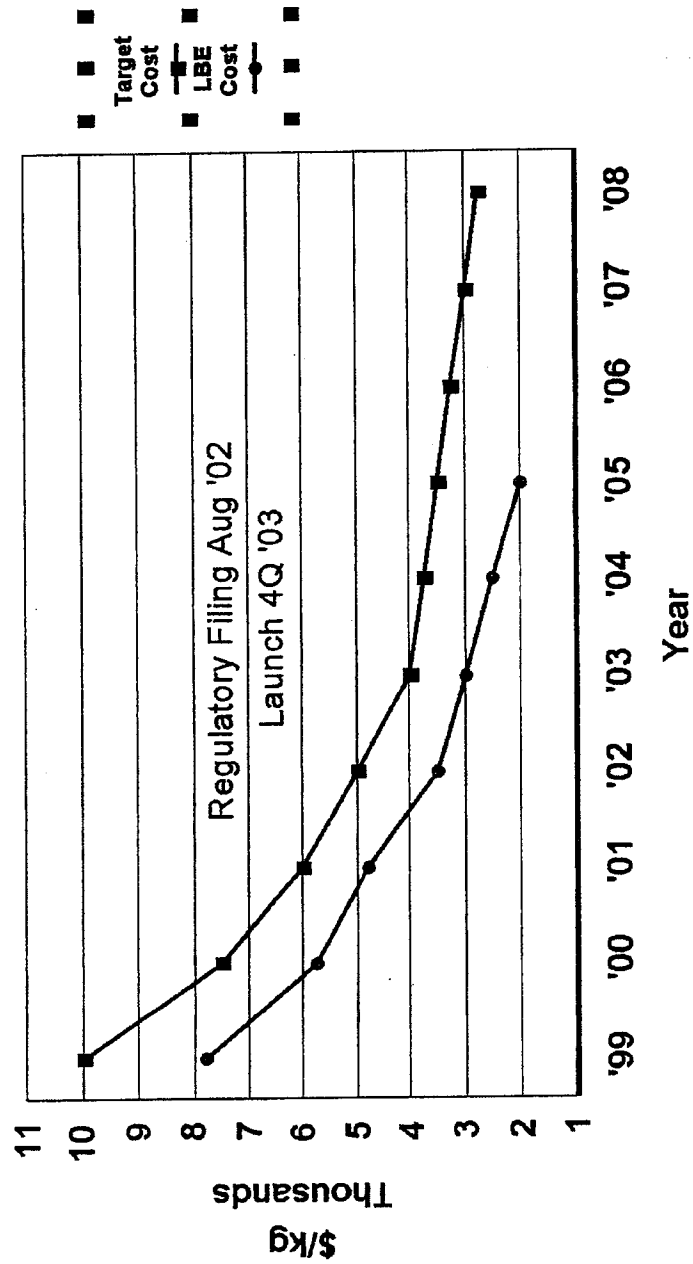
**Advantages:**

Commercial flexibility – additional manufacturers  
Process improvements (changes) without FDA prior approval  
Cost advantage

## **Bulk Drug Manufacturing**

*Projected Bulk Drug Costs*

Cost of Goods based on Current Process



**Bulk Drug Manufacturing**  
*Projected Annual Capacity, Single Site*

Bldg C7A/ NC	15MT
Bldgs C17 and C7A/ NC	50MT

**Alternative strategies:**

**Step 8 at vendor site(s)**

**Manufacturing in Abbott, Puerto Rico**

## ***Bulk Drug Manufacturing*** **Summary**

### **Summary**

- A viable process developed for commercial launch
- On track to achieve commercial target cost
- Identified strategies to meet long term bulk substance demand

***Tablet Key Issues***

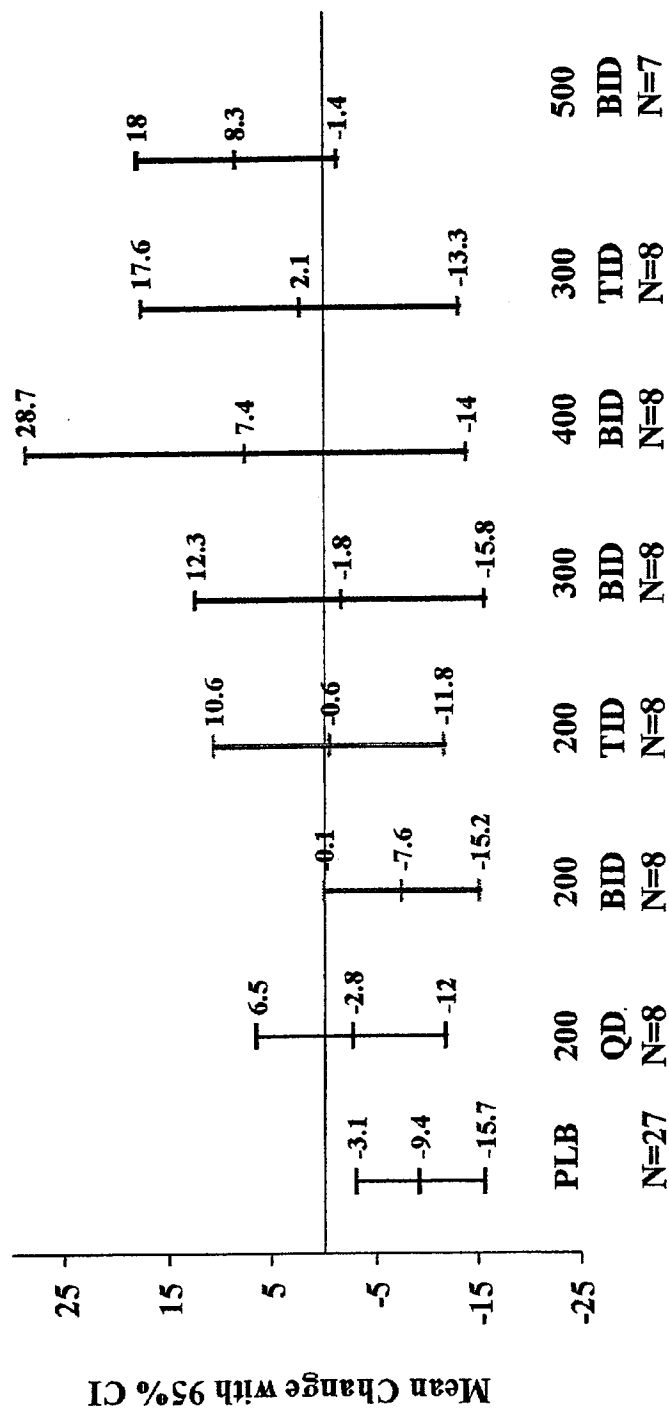
***QT Prolongation***  
***Dave Morris***

## ***Summary of ECG***

- A possible dose effect in Phase I at total daily dose  $\geq 800$ mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole.
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies.
- Will continue to monitor QT in Phase III programs.



**Mean Change of QTC  
(Multiple Rising Dose Study)**



### ***Multiple Rising Dose Study***

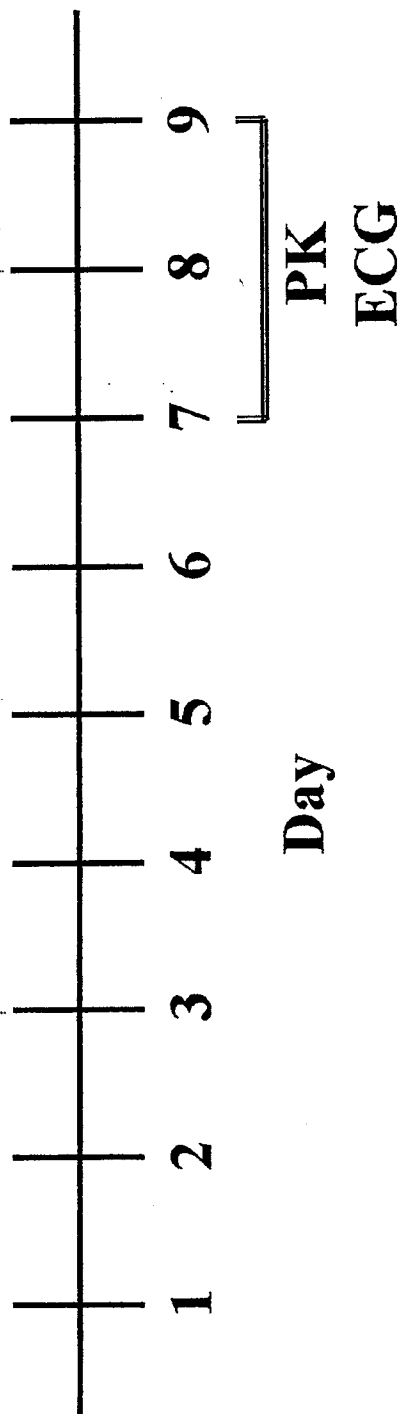
- No subject had QTc increase > 60 msec
- 3 subjects had QTc increase 30-60 msec ( $\geq 800$ mg/day)
- No subject had QTc of >500 msec
- No syncope observed

# ***Ketoconazole Interaction Study***

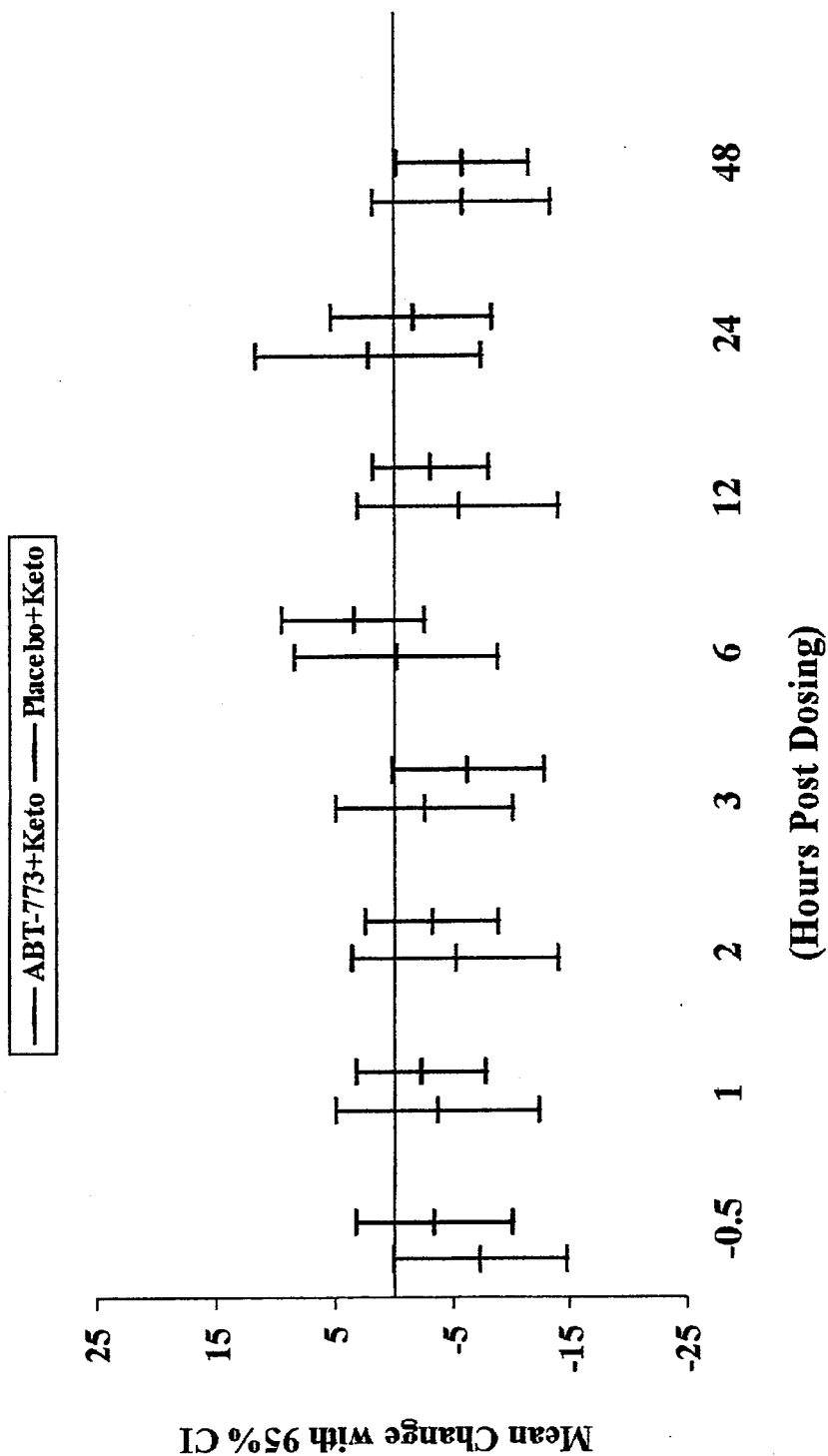
**ABT-773 or  
Placebo**

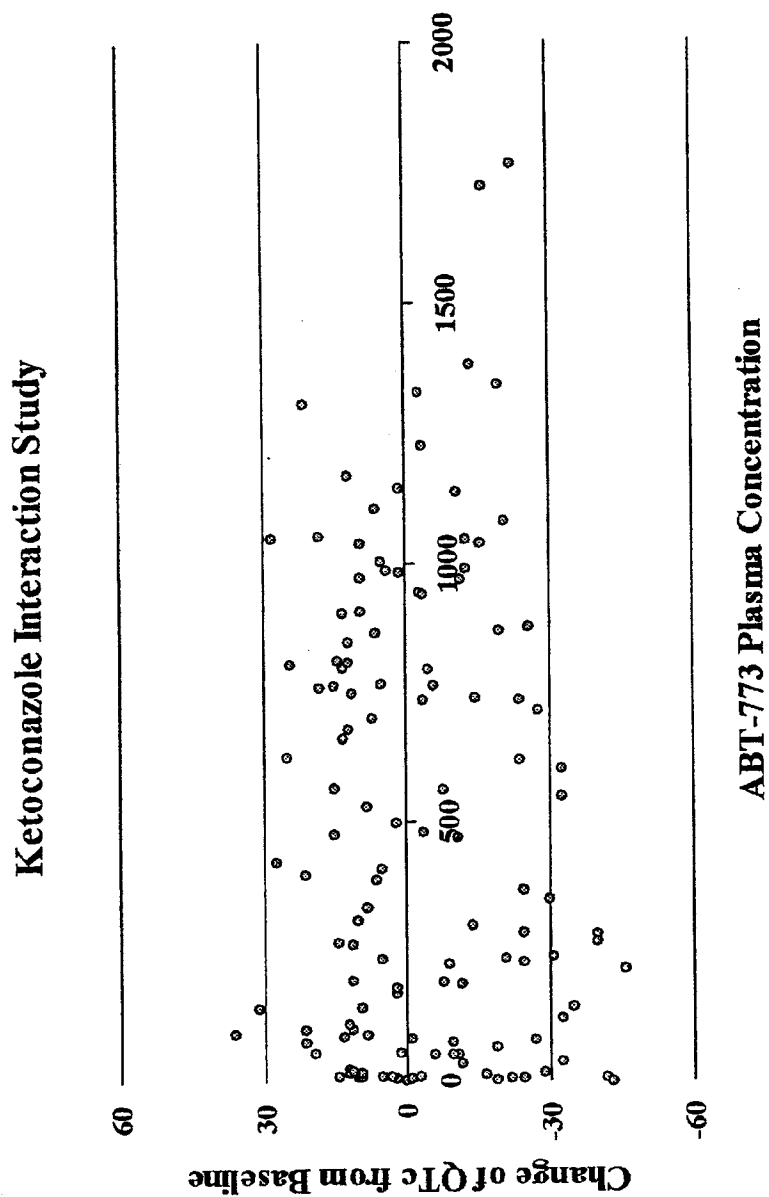
**ABT-773 or  
Placebo**

**Ketoconazole**



**Mean Change of QTC  
(Ketoconazole Interaction Study - N = 18)**

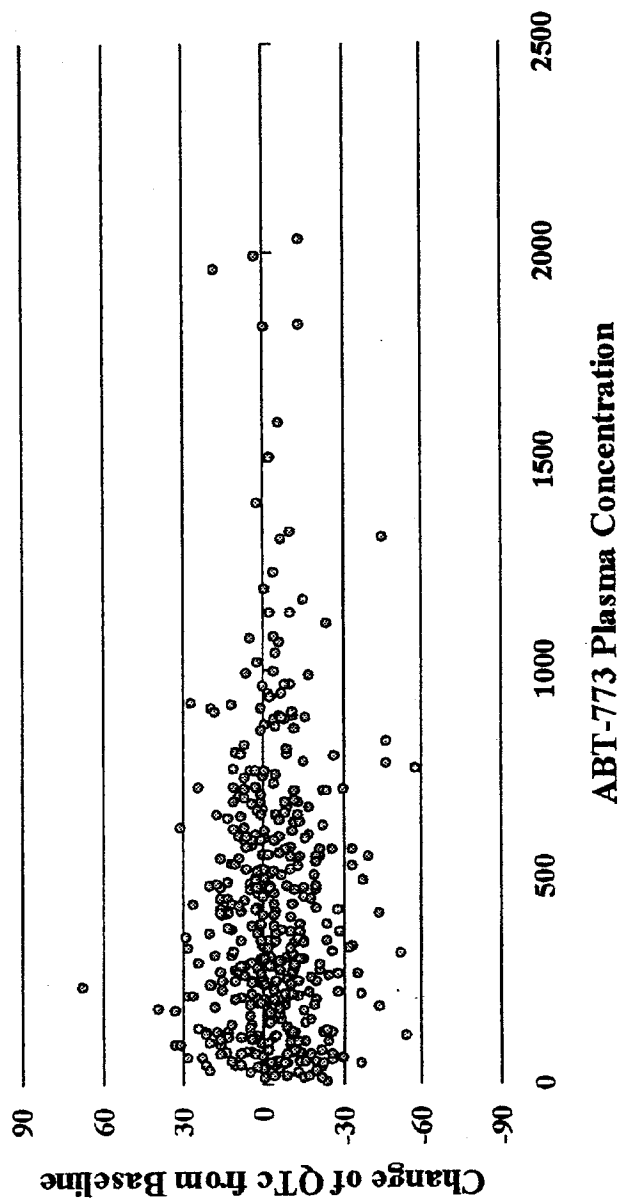




## ***Ketoconazole Interaction Study***

- No subject had QTc increase > 60 msec.
- 2 subjects had QTc increase of 30-60 msec.
- No subject had QTc of >500 msec
- No syncope observed

**Pooled Multiple Dose Studies  
( $\leq 300\text{mg/day}$ )**

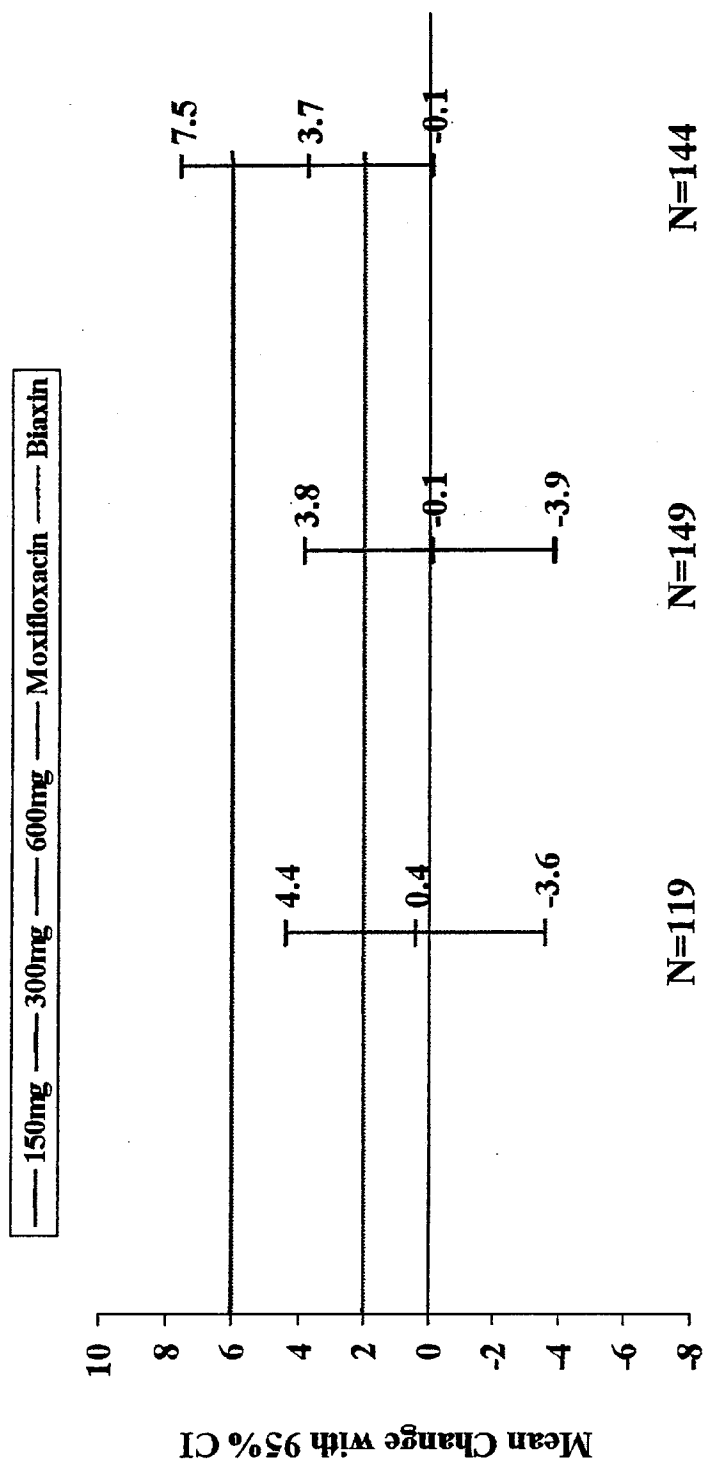


## ***All Phase I Studies***

- Total of 11 syncopes reported
  - 5 were pre-dosing
  - 6 were post-dosing
- All associated with blood draw



Mean Change of QTc from Pretreatment to During Treatment  
(Phase IIB - Based on Cardiologist Reading)



**Phase IIA/B**

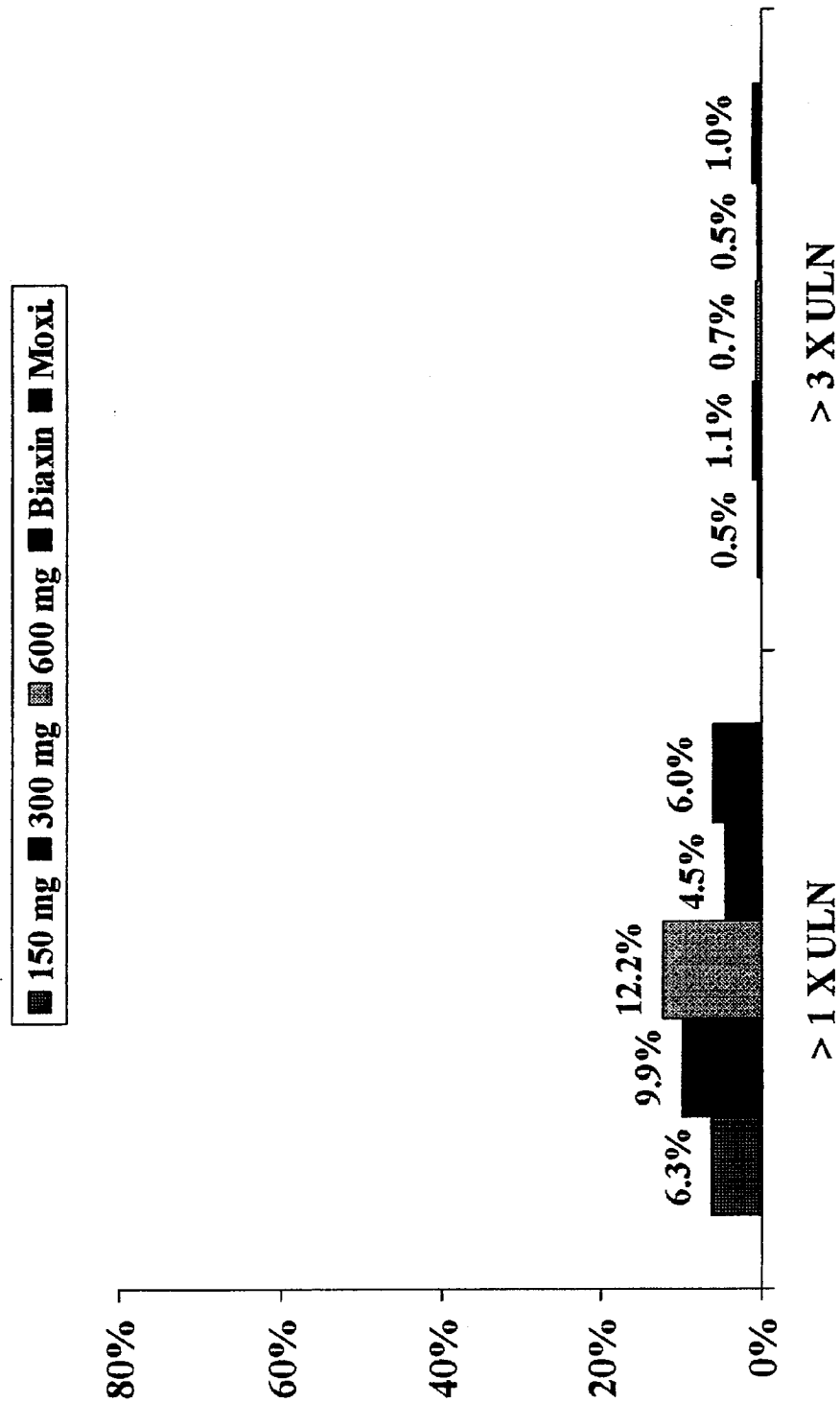
- 2 syncopes reported
  - 1 was immediately upon first dose on Day 1 (600mg QD)
  - 1 was 7 days post last dose (100mg TID)

***Liver Function  
Dave Morris***

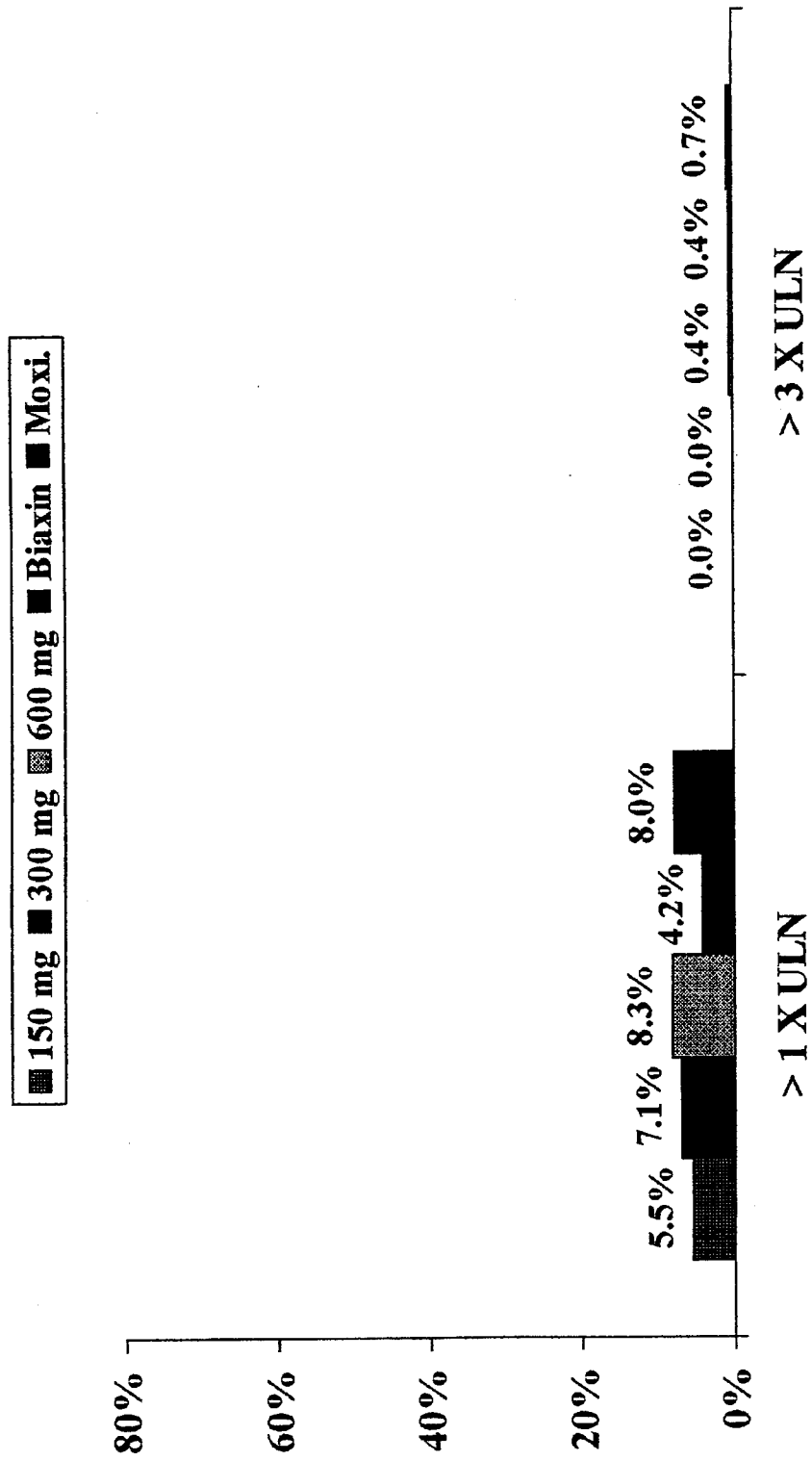
## ***LFT Summary***

- No evidence of LFT issue in Western subjects.
- No consistent evidence of dose response.
- Japanese bridging study results should be confirmed.
- Will continue to monitor LFT in Phase III programs.

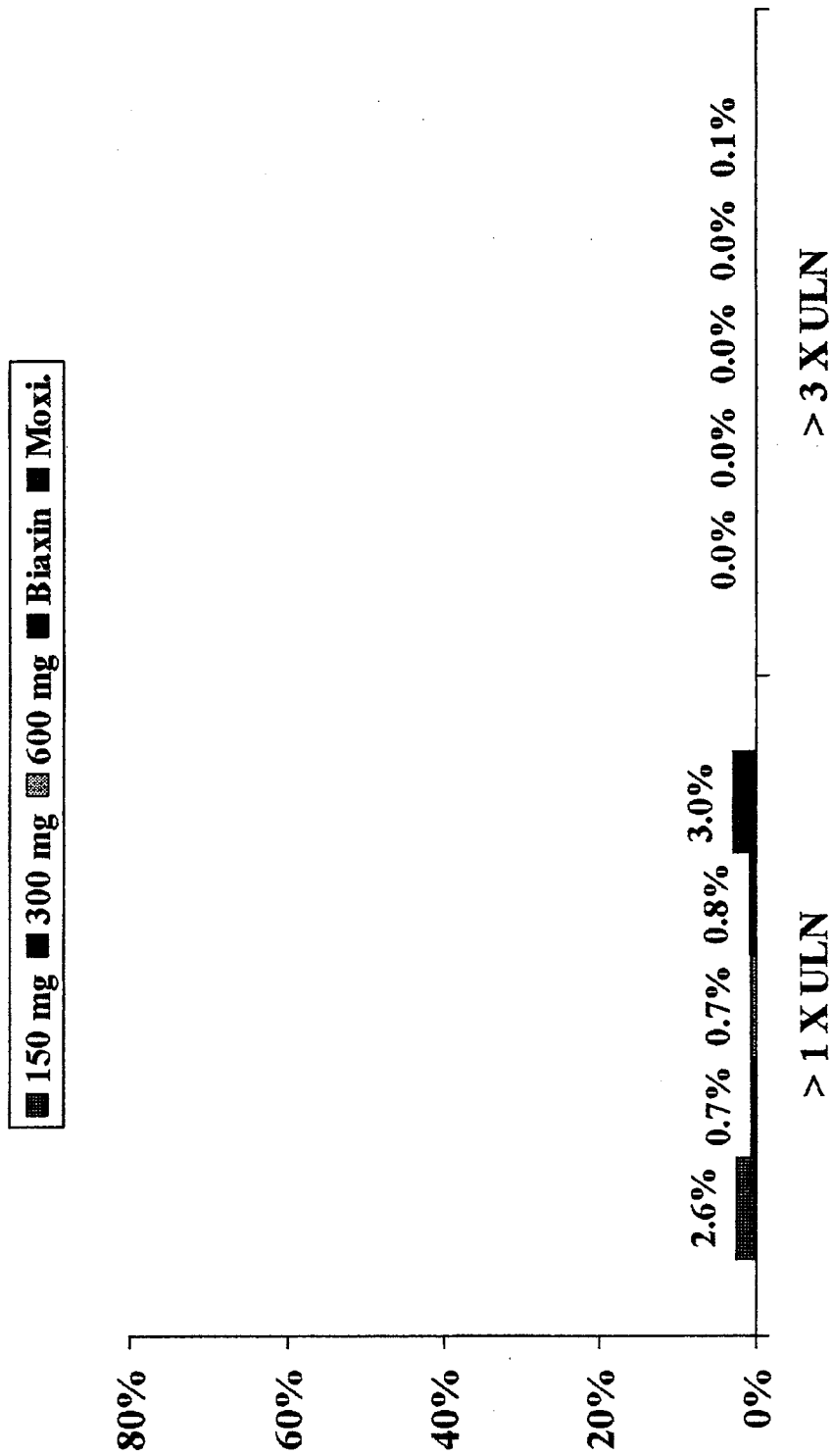
## Incidence Rate of SGPT Abnormalities



## Incidence Rate of SGOT Abnormalities



## Incidence Rate of Bilirubin Abnormalities



## Very high LFT Results: Phase II

	SGPT*	SGOT*	GGT\$	Alkaline Phosphatase*	Total Bilirubin&
<b>150mg QD</b>					
% (N)	0/181	<1% (1/192)	<1% (1/183)	0/200	0/201
95% UL	2% 3%	3%	2%	2%	
<b>300mg QD</b>					
% (N)	<1% (2/256)	<1% (1/267)	<1% (1/251)	0/278	0/288
95% UL	3% 2%	2%	1%	1%	
<b>600mg QD</b>					
% (N)	<1% (1/256)	<1% (1/263)	0/252	0/273	0/287
95% UL	2% 2%	2%	1%	1%	

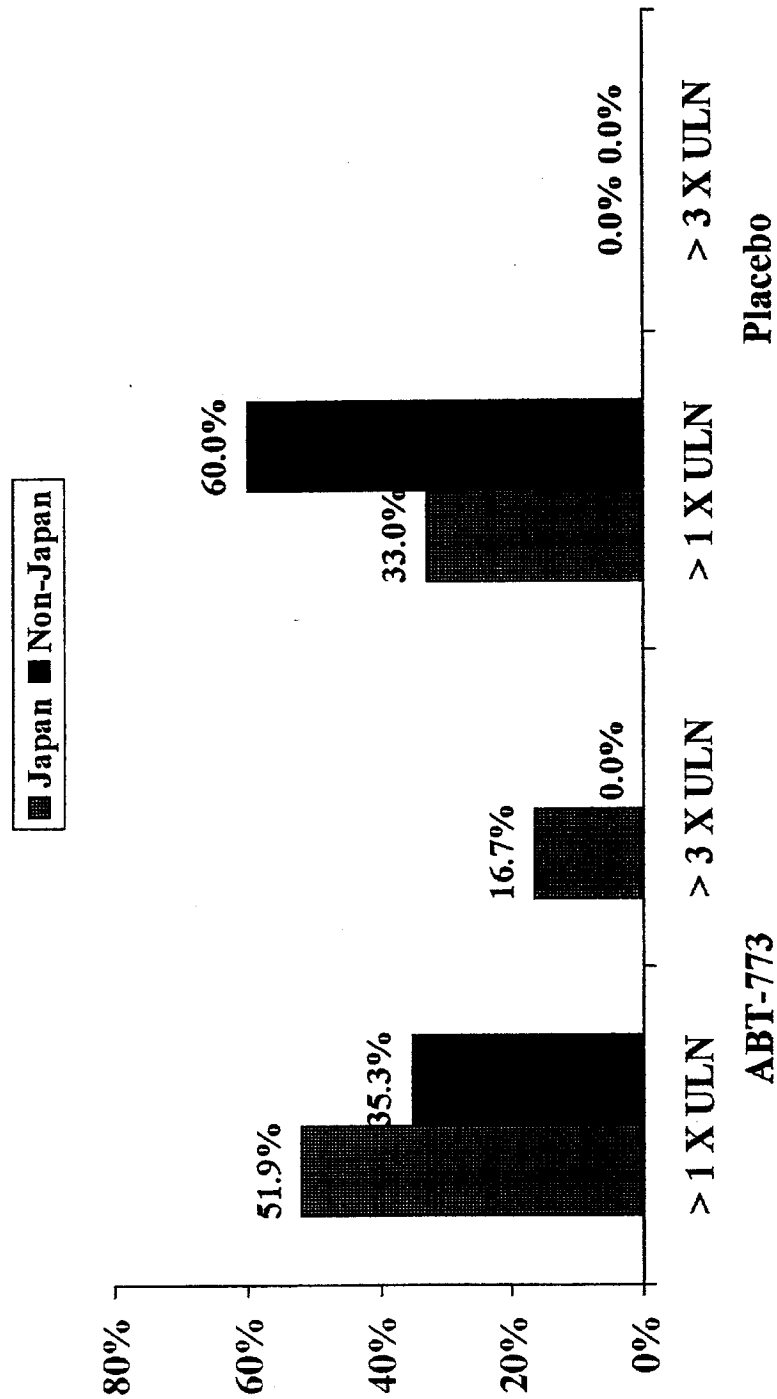
\*: &gt;= 3\*NUL

\$: &gt;= 5\*NUL

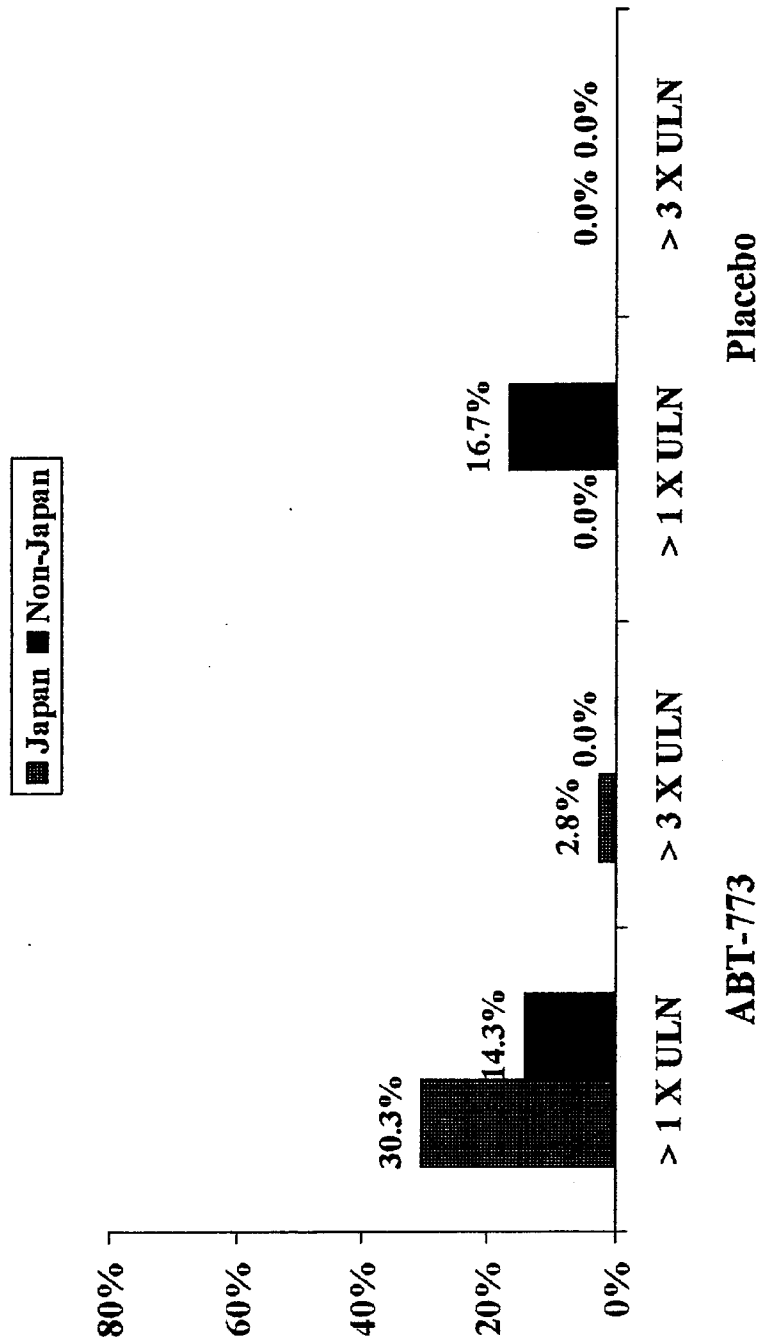
&amp; &gt;= 2 mg/dl.. Note: subject had normal LFT at baseline.



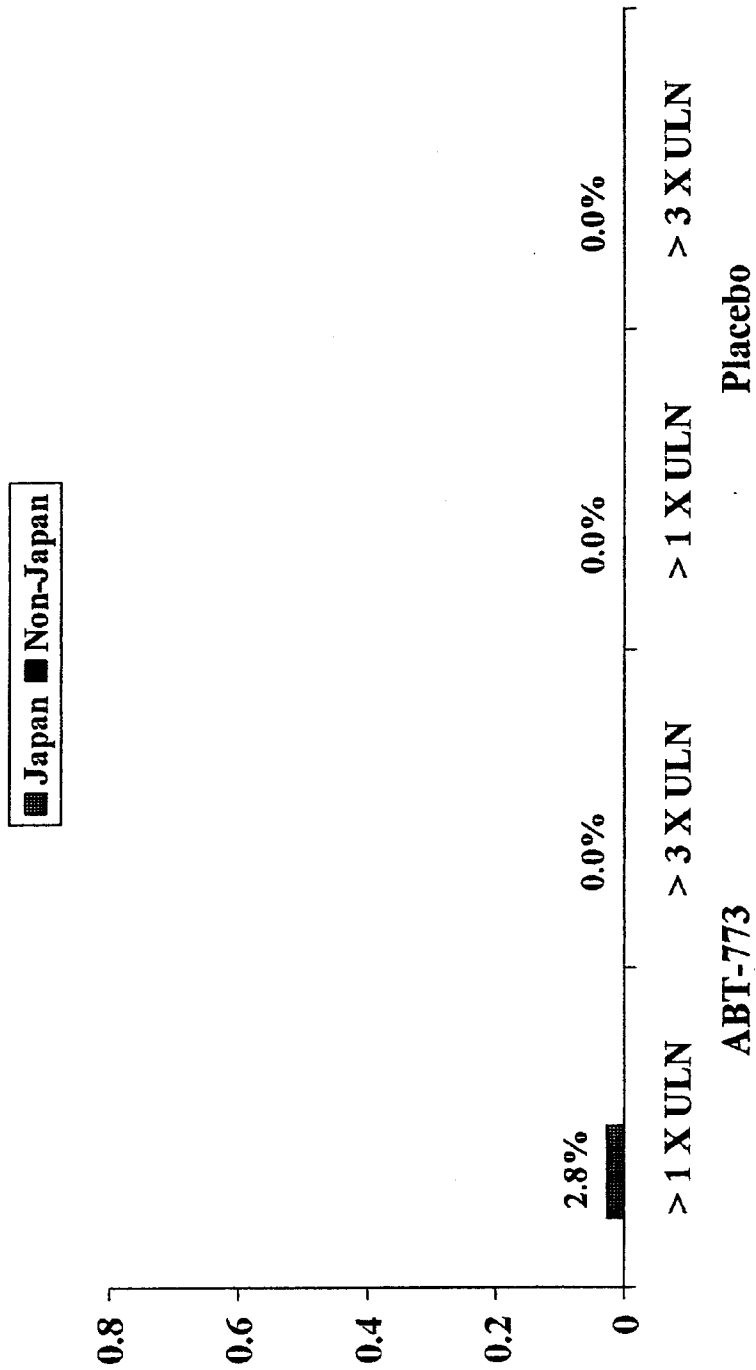
## Incidence Rate of SGPT Abnormalities Japan Bridging Study



## Incidence Rate of SGOT Abnormalities Japan Bridging Study



# Incidence Rate of Bilirubin Abnormalities Japan Bridging Study



**PK Profile**  
**Linda Gustavson**

***Regulatory  
Jeanne Fox***

## ***ABT-773 Regulatory Status***

- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting 11/27/00
- End-of-Phase 2 CMC FDA meeting target 1/01
- Tablet NDA submission target 8/02

## ***ABT-773 Regulatory Issues***

- **ABT-773 Potential for QT Prolongation**
  - QT issue is hot button for FDA
  - Question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QT
  - Required to include ECG monitoring in pivotal Phase 3 studies
- **ABT-773 Potential for QT Prolongation**
  - telithromycin (Ketek) data residing at FDA
    - Advisory Meeting scheduled for January
- **FDA may require a Phase 1 study in patients with underlying cardiac disease**
- **Some antimicrobials now contain warnings for QT prolongation**

## ***ABT-773 Regulatory Issues***

- **ABT-773 Potential for Liver Toxicity**
  - Ketolides similar to macrolides?
  - Request for additional dog tox work
  - telithromycin (Ketek) data residing at FDA
    - Advisory meeting scheduled for January
- **Plan to conduct routine liver monitoring in all Phase 3 studies**



## ***ABT-773 Regulatory Issues***

- Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of “macrolide-resistant *S. pneumo*”
- FDA will require “body of evidence”
  - excellent eradication of susceptible organisms
  - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients

## ***ABT-773 Regulatory Issues***

- **Miscellaneous**

- Based on NDA timing, potential good candidate for E-submission
- Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
- Timing of pediatric program and “due diligence” for formulation development critical

***Commercial Profile, Positioning & Financials***  
**Rod Mittag**

***I.V. Program  
Carol Meyer***

**ABT-773 IV Program**  
**Formulation Objectives**

- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counterion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.

## ***ABT-773 IV Formulation*** **Status**

- **PPD funded Program 01/00-08/00 (\$1.4MM)**
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- **HPD funded Program 08/00-12/00 (\$0.8MM)**
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program

***ABT-773 IV Formulation*****Animal Pain Study Results**

- Assessed 6 prototypes( 3 different counterions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
- Results not conclusive
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.

**ABT-773 IV**  
**Planned Clinical Program**

• Single Dose -rising Phase I study	Mar/01
• Multiple Dose Phase I with selected dose	June/01
• Initiate Phase III	Oct/01
– 2 step-down CAP studies (US/Europe)	
– 2-3 days dosing	
– Two seasons to complete	
• Filing	Aug/03



## ***ABT 773 IV Program Summary***

### **• Comments**

- Funding for '01 not available with PPD/HPD
- Go/No go could be made after Phase I based on safety profile(pain, QT, GI)
- Milestone funding recommended (\$MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant S. pneumo claim

***Pediatric Program***  
**Carol Meyer**

## ***ABT-773 Pediatric Program*** ***Formulation Objectives***

- **Develop coated particle formulae for global use**
  - Formulate coated particles for Suspension - 150mg/5mL & 300mg/5mL
  - Formulate coated particles as a dry syrup, sprinkle or sachet.
- **Desired Properties**
  - Once a Day Dosing
  - Acceptable 'Initial Taste'
  - Minimal 'After Taste'
  - No Unpleasant Mouth-feel
  - Acceptable Color and Flavor
  - No Refrigeration Required.

**ABT-773 Pediatric Program**  
**Status**

- |   |         |
|---|---------|
| • Initiated January 2000                                    |         |
| • 2000 Funding through first PK study milestone only (\$MM) |         |
| • Prototype Development completed (granules for suspension) | May '00 |
| • Phase I Single Dose Study - 2 prototypes completed        | Aug '00 |
| • First set of Taste Evaluations completed                  | Sep/00  |
| • Comparative Taste vs Clari and Azi                        | Dec/00  |

**ABT-773 Pediatric Program**  
*Formulation Trade-off*

**ABT-773 Pediatric - Reconstitutable Suspension**

Taste / Cost



Bioavailability

## ***ABT 773 Pediatric Program Challenges***

### **• Pharmacokinetic Profile (plasma, middle ear fluid)**

#### **• Taste**

- Masking Bitter Taste
- Flavor
- Mouth-Feel

#### **• Preserving the Reconstituted Suspension**

#### **• Ease of Manufacture**

#### **• Cost**

**ABT 773 Pediatric Program**  
*Formulation Development*

**• Formula Selected**

- Zein Coated Stearine 07 Based Particles
- Formula acceptable both from an Organoleptic and Dog Bioavailability standpoint
- Two prototypes
  - Same core
  - Different coating levels (15% and 25% coating)

***ABT 773 Pediatric Program***  
Taste Assessment

- **Taste Assessment conducted by Arthur D Little**
  - Utilized a Flavor Profile Method of Sensory Analysis
- **Task 1: Sensory Analysis of Aqueous Solutions/ Suspensions of Uncoated Drug Substances**
  - ABT-773
  - Clarithromycin (Biaxin®)
  - Azithromycin (Zithromax®)
- **Task 2: Sensory Analysis of Coated ABT-773 Prototypes**



## ***ABT 773 Pediatric Program***

### **Taste Assessment**

### **Sensory Analysis of Uncoated Drugs**

#### **Summary of Results**

*The three drug substances can be ranked from most to least bitter as follows:*

<b>Drug Substance</b>	<b>Concentration (mg/mL) Exposure in Initial Bitter Intensity Scale (Subject)</b>
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

- ABT-773 is approximately five times more bitter than clarithromycin

***ABT 773 Pediatric Program***  
Taste Assessment

- **The flavor quality of the two coated drug prototypes was similar—the bitter intensity was moderate-to-strong initially and throughout the aftertaste.**
  - The observed bitter intensity is well above the “consumer concern level” of a slight intensity.
  - We believe that the lingering bitterness results from the “sustained release” of drug from the coated drug particles that lodge in the oral cavity (both prototypes exhibited a moderate amount of grittiness).

# **ABT 773 Pediatric Program** Phase I PK Results

- The AUC ratio (suspension:tablet) is 75% and the Cmax ratio is 77 to 79% for the two suspension formulations (SC-1a and SC-1b) respectively.

Pharmacokinetic Parameters	Tablet (N = 42)	Suspension (SC-1a) (N = 41)	Suspension (SC-1b) (N = 41)
Tmax (h)	3.0 ± 1.3	2.6 ± 1.0	2.8 ± 1.0
Cmax (ng/mL)	628 ± 263	505 ± 234	494 ± 223
AUC <sub>∞</sub> (ng•h/mL)	4527 ± 1830	3645 ± 2226	3521 ± 1868
t <sub>1/2</sub> (h)‡	6.3	6.8	6.7
Cmax Ratio (test/ref)*	---	0.79	0.77
AUC <sub>∞</sub> Ratio (test/ref)*	---	0.75	0.75

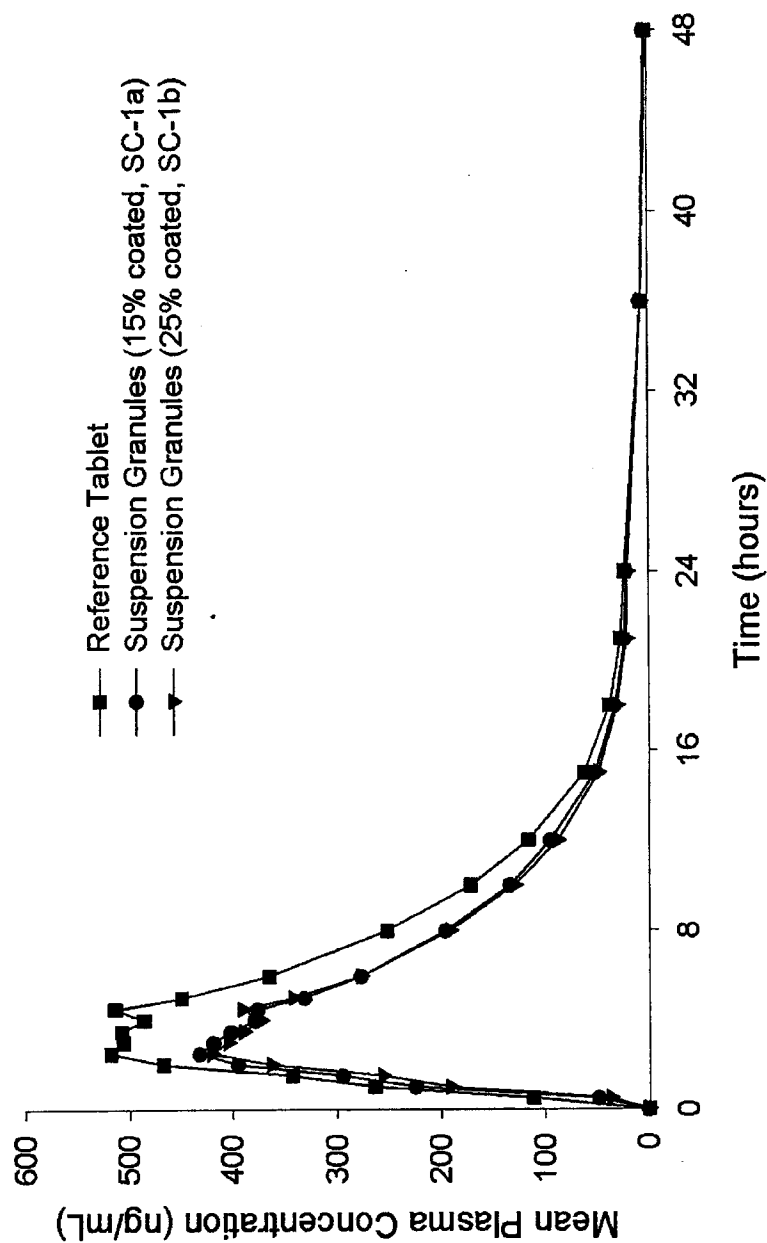
‡ Harmonic mean.

\* Geometric mean

# ABT 773 Pediatric Program

## Phase I PK Results

Study M00-196: Preliminary Mean ABT-773 Plasma Concentration-Time Profiles



***ABT 773 Pediatric Program***  
Proposed Clinical Program

<b>Proposed Pediatric Clinical Studies for Registration (Phase 1, 2, 3)</b>			
<b>Indications/Type</b>	<b>Phase</b>	<b>No. of Studies</b>	<b>No. of Subjects</b>
PK adult single rising dose, multiple rising dose/effect of food	1a 1b	4	96
Otitis Media (dose ranging), PK in children	2	1	100
Otitis Media, Pharyngitis, CAP	3	6	1800

***ABT 773 Pediatric Program***  
Proposed Clinical Program

- **First option**
  - Develop a pro-drug with no immediate after taste , stable in a suspension formulation , hydrolyzed in acidic pH and absorbed as parent drug.
  - Three pro-drugs under study (benzoyl,TMB,ES)
- **Second option**
  - Continue improving after taste,PK of parent drug formulation.
- **Recommend first option with Go/No go in 06/01 (\$MM)**

**Japan Program**  
**Carol Meyer**

## ***Japan Program***

***Taisho***

- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan
- Findings in first PK trial in Hawaii resulted in repeat of Phase I in Japan



## ***Japan Program***

### ***Phase I Findings***

- Initial Phase I study conducted in Hawaii with Japanese and non-Japanese subjects
- Results indicate 50% higher AUC and Cmax in Japanese vs non-Japanese
- Liver enzyme elevations were noted in a few Japanese subjects, however it was not dose related
- Decision made to repeat Phase I in Japan

## **Japan Program**

### ***Clinical Plan***

<b><u>Start</u></b>	
Nov/00	<ul style="list-style-type: none"><li>• <b>Phase I in Japan</b><ul style="list-style-type: none"><li>– Food Effect Study</li></ul></li></ul>
Dec/00	<ul style="list-style-type: none"><li>– Single and multiple dose study</li></ul>
April/01	<ul style="list-style-type: none"><li>– Review data (Abbott/Taisho)<ul style="list-style-type: none"><li>• PK data Japanese vs Caucasian</li><li>• Development program strategy</li></ul></li></ul>
May/01	<ul style="list-style-type: none"><li>– Present Kiko data and recommend development program</li></ul>
2Q/01	<ul style="list-style-type: none"><li>– Start Tissue Conc. Study</li></ul>

## ***Japan Program***

### ***Clinical Plan***

- **PK similar in Japanese and Caucasians (12/02 filing)**
- **Recommend to Kiko same dose in Japan as in ex-Japan**
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in SSS, Dentistry, Otolaryngology, UTI and pan- bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- **PK different in Japanese and Caucasians(12/03 filing)**
  - Phase II dose ranging study in CAP (Bridging study)
  - -Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing

**Summary**  
**Carl Craft**

## ***Backups***

**Competitive Update, Ketek-Rod Mittag  
OS/IV/overall financials-Rod Mittag**

***IV/OS/Overall Financials***

**Rod Mittag**



## **Deposition Exhibit 8**

### **P's Exhibit IL**



[illegible]

**HIGHLY CONFIDENTIAL**  
**ABBT 0000387**

February 2001

ABT-773

## Monthly Highlights – Key Project Progress

- All Phase III U.S. studies are actively enrolling patients. Drug releases have started for the European studies with 9 sites ready to enroll in CAP, 3 sites in ABS, 21 sites in ABECB and 11 sites in ASP. No patients have been enrolled in Europe since the initial drug shipments have been made (within the last 2 weeks). We are expecting enrollment in all four studies at any time. All sites are being very carefully managed to get them actively enrolling patients as soon as possible.
- Further Phase III start up activities are ongoing in Central America, So Africa and So America for CAP and ABS for their winter seasons starting in May. As we proceed with the enrollment in the Northern Hemisphere during March and April, we will make a firm decision on initiating these sites for enrollment to be as cost effective as possible.
- The initial Phase I study for the IV formulation will go ahead and is planned to start in early May. This study will enable us to evaluate the appropriate IV dose and evaluate injection site pain with the formulation prior to a Multiple Dose study. Timing for Phase I Go/No Go by September is critical if we would like to have an IV filing within a year of the tablet filing.
- The CMC and Biopharm End of Phase II package was submitted to FDA on March 1st to request a meeting in April. Meeting preparations are in progress.
- A CMC planning meeting with Taisho and Dainabot is scheduled for March 7 and 8<sup>th</sup> to discuss the timing and requirements for the Japanese Phase II/III clinical supplies and Japanese NDA filing requirements to include these activities in the Abbott Park and U.K. CMC plans.
- A team review was held to discuss all data gathered on the pediatric formulation prototypes. The final taste testing comparing 773 to clari and azi suspensions indicated that the 773 prototype had a better taste than the clari suspension. A follow up meeting will be held with the franchisee to discuss further interest in pursuing a pediatric formulation.

## Next Quarter's Key Progress Markers

Key Progress Marker	Target Date
Hold CMC/Biopharm End of Phase II meeting with FDA.	04/30
Determine if Southern Hemisphere sites for CAP and ABS should be initiated as a contingency if US/European enrollment fails to meet 500 patient target.	04/30
Complete enrollment in CAP and ABS Dose selection studies to meet Dose Decision milestone in July, assuming US/Europe can meet 500 patient target.	06/01
Complete enrollment in ASP and ABECB comparator studies in the U.S.	06/01
Complete intermediate scale-up activities in the U.K. site for initial bioequivalence study between Abbott Park and U.K. mfg sites.	05/31
Initiate first Phase I study of IV formulation.	05/01
Results available for Japan Phase I Dose Ranging study to determine Japan dose for Phase II/III studies and potential Bridging strategy.	04/15
Hold Abbott/Taisho meeting to discuss Japan Phase I results and propose Phase II/III clinical plans to discuss with KIKO.	05/08

HIGHLY CONFIDENTIAL

February 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and describe impact	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
A change in bulk drug physical or chemical properties during formulation development.	<input type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Delay in the Aug 2002 filing date. If at the 1200L scale, a delay of up to 18 months.	A strategy for the bulk drug lots that will be used in the NDA formulation runs will be reviewed with the CMC Technical Committee in early December. Bulk drug properties and granulation variables are being evaluated as a means to develop appropriate physical specifications for the bulk drug.	SPD/PARD	12/2001
Clinical enrollment challenges due to a) delay in end of phase II meeting from September to November at request of FDA b) delay in start of study due to protocol changes requested by FDA c) light 2000-01 flu/respiratory season	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Critical path trials to development timeline are CAP & sinusitis, with dose decision for these indications needed by 7/2001 to maintain current timeline. Current estimates are that 7/2001 decision will be met.	Meeting with FDA was held on November 27 <sup>th</sup> . Protocol amendments have been signed off incorporating all FDA requested changes and implemented in the U.S. and Europe. Additional sites added in Europe and southern hemisphere to make up for delays. The team is working to overcome the challenges as much as possible by closely managing clinical sites in the U.S. and Europe, as well as planning for contingency sites in the Southern Hemisphere. A decision to initiate the Southern Hemisphere sites will be made in April as a contingency should the US and Europe fail to meet enrollment targets for CAP and sinusitis. ASP and ABECB studies are not on the critical path. Current estimates are that 7/2001 decision will be met.	Venture	7/2001
150 mg QD vs BID dose decision in CAP/sinusitis.	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing, while relatively minor commercial impact ex-US, represents significant commercial hurdle in US.	Decision must be made in light of QD vs BID CAP and sinusitis data (7/2001); DSG analysis is planned to facilitate decision; internal efforts to defend 150 mg QD dosing with data on potent ribosome binding properties of ABT-773 are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study.	Venture/NPD/DSG	7/2001

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February 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product.	QT effects are the current hot topic for the FDA, and were reflected in the changes they requested to the Phase III program. FDA concern is whether ketolides behave like macrolides and whether there may be a class effect. FDA requested an acute tox study in dog to further evaluate cardiac effects and also discussed whether a Phase I study should be conducted in subjects with underlying cardiac disease. ECG monitoring will be done in all Phase III studies with the exception of the ASP study in Europe.	Regulatory	6/2002/
Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch.	<input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Ability to define step 5 as the starting material will allow us to make further process improvements to reduce the cost of the bulk drug.	The End of Phase II CMC meeting with FDA will be requested for January 2001 to present the package on starting material definition for step 5 intermediate. Meeting is targeted for the end of March. The end of Phase II package outlining our plans for starting materials was submitted to FDA on March 1.	SPD	04/2001
The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially, particularly with respect to H. influenzae.	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Support by PK/PD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model.	Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. Dose decision for CAP & sinusitis expected 7/2001. To address this issue and potentially create a new model for evaluating PK/PD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study.	Venture/NPD	07/2001

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ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input type="checkbox"/> Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim.	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .		FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required. CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim. <b>The Phase I study to evaluate the IV formulation prototype will initiate in May 2001.</b>	Venture	06/2002
Due to the dose change in the base development program, Phase I will be repeated in Japan to further evaluate dose-ranging. An increase in liver enzymes was observed in the low and medium dose groups of Japanese volunteers in the first study in Hawaii, and will be further evaluated in the Phase I studies done in Japan. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period. The Japanese BAL study will start in April. Dose selection and BAL results need to be available prior to a meeting with Kiko to discuss the Phase II/III strategy. The current decision is to proceed to the KIKO meeting once Phase I results are available and a dose selection decision has been made for CAP and ABS based on the US/European studies. Preliminary BAL results may be available in August.	Japan	08/2001/

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Key Project Issues and Risks				
Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed.	<input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding.	HPD funding for 2001 (\$7MM) is no longer approved. At the ABT-773 Portfolio meeting, Jeff Leiden committed to find funding (approx. \$1MM) to do the Phase I studies for the IV in 2001 to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements. Decision was made by John Leonard to proceed with the initial Dose Ranging Phase I IV study. This is planned for early May. A Go/No go decision on the IV formulation is planned for Sept. 2001.	HPD, Venture	09/2001

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## Key Activities

Commercial		Formulation		Plan Date: 12/98	
Activity	LBE	Activity	Plan	Actual	
Completion of study tracking intranet	1001	Phase I Formulation (Caps)*	12/1997	12/1997	
Integration of intranet into communication plan	2001	Phase II Formulation (Tablet)	7/1999	8/1999	
Integration of intranet into draft product label	2001	Clinical Supplies Phase IIB	7/1999	8/1999	
Identification of communication vendor	2001	Phase III Formulation (Tablet)	4/2000	7/2000	
Submission of brand/USAN names	2001	Phase III Clinical Supplies Manufactured	9/2000	9/2000	
Preliminary qualitative positioning research	4001	NDA Lots (3) Completed	7/2000	01/2001	
Quantitative market research to support revised forecast	4001	Completion of 1 Year Stability for NDA	8/2001		
Preliminary qualitative positioning research	4001	Formulation Peer Review	11/2001		

Drug Substance		Toxicology		Plan Date: 12/98	
Activity	KG	Plan Start 7/Date??	Actual Start Date	Report Completed	
2-week oral Rat/Monkey		7/1997	8/1997	9/1998	
Acute Studies		8/1997	8/1997	12/1997	
Mouse Lymphoma/Micronucleus		11/1997	11/1997	4/1998	
1 Month Rat/Monkey		12/1997	12/1997	12/1998	
Pregnant Rat/Rabbit HF		1/1998	1/1998	11/1998	
SEG II Rat/Rabbit		3/1998	3/1998	2/1999	
Guinea pig sensitization		11/1998	11/1998	2/1999	
3 Month oral Rat/Monkey		8/1999	10/8/1999	8/2000	
Seg I/III Rat		8/1999	10/8/1999	12/2000	
IV Irritation studies, set 1		7/1999	7/15/1999	8/1999	
IV Irritation studies, set 2		2/2000	2/2000	3/2000	
IV 2-week Rat/Monkey Studies		6/2000	6/2000	01/2001	
Neonatal/Juvenile Rat		10/1999	11/1999	7/2000	

See the Following page for a  
summary of Bulk Drug  
deliveries in SPD.

\* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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SPD ABT-773 Bulk Drug Deliveries Update						
	Target Date	Amount	Delivery Date	Amount	Lot #	Amount after milling
Campaign 1	2/28/99	200 Kg	2/23/99	209 Kg	50-007-CA-00	207.5 Kg (2/26)*
Campaign 2a	6/15/99	140 Kg	6/17/99	131 Kg	54-702-NI-00	129.4 Kg (6/19)*
Campaign 2b	7/15/99	140 Kg	7/21/99	121.5 Kg	55-208-CB-00	119.3 Kg (8/4)*
Tox lot	8/30/99	5 Kg	8/25/99	6.1 Kg	55-718-NI-00	
Campaign 3a	9/30/99	160 Kg	10/8/99	170.5 Kg	58493CB00	138.4 Kg (10/16)*
Campaign 3b	10/21/99	160 Kg	10/11/99	176.5 Kg	58494CB00	169.5 Kg (10/16)*
Pilot run 1	*****	15 Kg	10/30/99	18.9 Kg	59763N100	no milling
Pilot run 2	*****	15 Kg	2/5/00	15.5 Kg	61790NI00	no milling
Pilot run 3	*****	25 Kg	1/30/00	27.5 Kg	62764CB00	27.3 Kg (4/18)*
Campaign 4	12/10/99	320 Kg	11/23/99	355 Kg	61741CB00	309 Kg (3/2)*
Campaign 5	12/30/99	300 kg	12/16/99	300.5 Kg	60865CB00	269.2 Kg (3/3)*
Campaign 6	2/28/00	280 Kg	2/23/00	321 Kg	62796CB00	315.5 Kg (3/6)*
Campaign 6 (IV)	2/28/00	15 Kg	2/22/00	20 Kg	62797CB00	18 Kg (3/15)*
Campaign 7	3/30/00	300 Kg	4/10/00	370 Kg	63890CB00	361.2 Kg (4/18)*
Campaign 7 (IV)	3/30/00	5 Kg	3/29/00	19 Kg	63889CB00	17.2 Kg (4/11)*
Campaign 8	4/25/00	200 Kg	5/11/00	263 Kg	64970CB00	256.5 Kg (5/15)
Campaign 8 (IV)	4/25/00	15 Kg	4/25/00	19.8 Kg	64971CB00	17.7 Kg (5/11)*
Campaign 9	6/15/00	300 Kg	6/14/00	375.7 Kg	65064CB00	355.7 Kg (6/20/00)
Campaign 9 (IV)	6/15/00	15 Kg	6/5/00	18.1 Kg	65065CB00	16.7 Kg (6/9/00)*
Campaign 10	7/15/00	300 Kg	7/26/00	361.2 Kg	67176CB00	359.0 Kg (8/10/00)
Campaign 11	8/15/00	300 Kg	8/4/00	333.7 Kg	68285CB00	271.9 Kg (9/7/00)
Campaign 12	10/6/00	300 Kg	9/27/00	356 Kg	69458CB00	292.3 Kg (12/8/00)
Campaign 13	11/23/00	300 Kg	11/15/00	351.2 Kg	71665CB00	349.1 Kg (12/20/00)
				Total (year 2000)	2,815.5 Kg	
Campaign 14	1/29/01	300 Kg	1/26/01	327.5 Kg	73886CB00	318.9 Kg (02/13/01)
Campaign 15	2/10/01	330 Kg	1/14/01	354.9 Kg	71699CB00	353.8 Kg (02/02/01)

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• Weight after rework

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*All Clinical Studies:*

Protocol Number	Phase	Study Name	Protocol Number	Phase	Study Name	Start 1 <sup>st</sup> Pt. Dosed	End (Last CRF In)	Patients		Start 1 <sup>st</sup> Pt. Dosed	End (Last CRF In)	Patients	
								Target	Current			Target	Current
M89-048	II	Dose Ranging, ABECB				9/1/99	3/31/00	300	384				
M89-053	II	Dose Ranging, Sinusitis				9/1/99	4/30/00	300	292				
M89-054	II	Dose Ranging CAP				9/1/99	4/30/00	300	187				
M00-219	III	CAP, Dose Ranging				11/7/00	4/30/01	800	127				
M00-216	III	ABECB vs Azithromycin				11/7/00	4/30/01	600	230				
M00-217	III	ABECB vs Levofloxacin				11/7/00	4/30/01	500	0				
M00-225	III	Sinusitis Dose Ranging				11/7/00	4/30/01	600	190				
M00-223	III	Pharyngitis vs Penicillin 250mg TID				11/7/00	4/30/01	520	300				
M00-222	III	Pharyngitis vs Penicillin 500mg TID				11/7/00	4/30/01	520	0				

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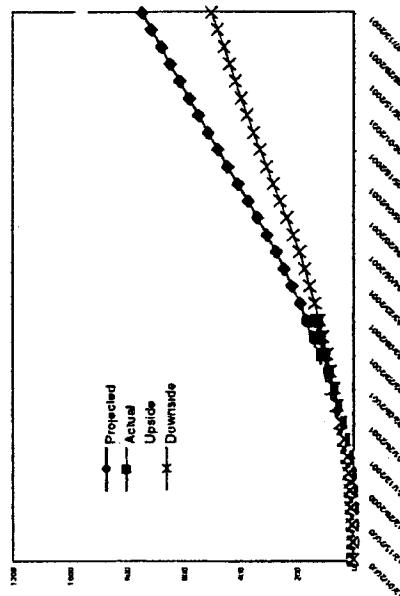
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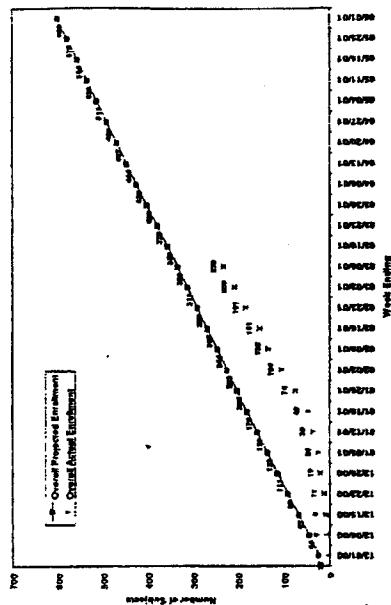
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**February 2001****ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

<b>Protocol:</b>	<b>M00-219 – Dose-Ranging CAP</b>	<b>M00-216 – Phase III ABECB vs Azithromycin</b>
<b>Objective:</b>	Dose selection.	Safety & Efficacy
<b>ABT-773 Doses:</b>	150mg QD vs 150mg BID, 10 days	150mg QD, 5 days
<b>Comparator Doses:</b>	None	Azithromycin 500mg day 1, 250mg QD for 4 days
<b>Target Enrollment:</b>	800	600
<b>Status:</b>	Currently enrolling	Currently Enrolling
<b>Major Findings:</b>		



Author:  
(Double click on chart to edit)



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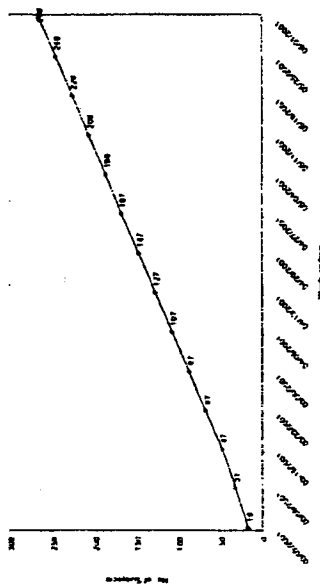
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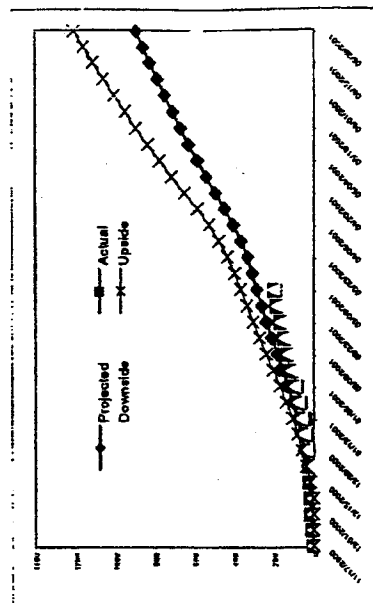
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**February 2001****ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

<b>Protocol:</b>	<b>M00-217 - Phase III ABECB vs Levofloxacin</b>	<b>M00-225 - Sinusitis Dose-Ranging</b>
<b>Objective:</b>	Safety & Efficacy	Dose Selection
<b>ABT-773 Doses:</b>	150 mg QD	150mg QD vs 150mg BID, 10 days
<b>Comparator Doses:</b>	Levofloxacin 500mg QD for 7 days	None
<b>Target Enrollment:</b>	500	600
<b>Status:</b>	Enrollment not yet started.	Currently enrolling
<b>Major Findings:</b>		



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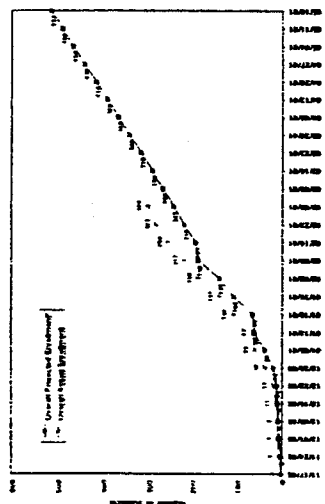
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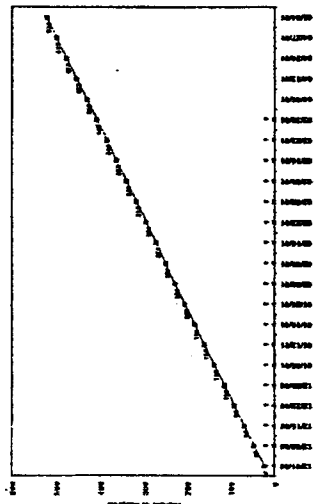
ABT-773

**Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

<b>Protocol:</b>	<b>M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID</b>	<b>M00-222 - Phase III Pharyngitis vs Penicillin 500mg TID</b>
<b>Objective:</b>	Safety & Efficacy	Safety & Efficacy
<b>ABT-773 Doses:</b>	150mg QD., 5days	150mg QD, 5 days
<b>Comparator Doses:</b>	Penicillin 500 mg TID, 10 days	Penicillin 500mg TID, 10 days
<b>Target Enrollment:</b>	520	520
<b>Status:</b>	Currently enrolling	Sites initiated, enrollment not yet started
<b>Major Findings:</b>		



Author:  
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## **Deposition Exhibit 9**

### **P's Exhibit IO**

**ABT-773 Update February 12, 2001****Introduction**

ABT-773 is a ketolide antimicrobial, an evolutionary step from the macrolide antimicrobials such as erythromycin and the new generation macrolides like clarithromycin and azithromycin. It is in phase III development as a replacement to clarithromycin.

The antibiotic market is a large market (\$20.5 Billion in 1999) and is expected to expand on a global sales basis (\$26.5 Billion in 2005). The majority of the markets sales are in the oral tablet/capsule segment. Market sales increases are being driven by replacement of older/cheaper agents with branded agents. Zithromax has driven market demand for cost/convenience/tolerability, while the quinolones (Levaquin, Tequin, Avelox) are the fastest growing segment, playing into resistance concerns. Resistance is a major driving force for both the quinolones and ketolides development.

**Ketolides are a Novel Class of Antimicrobial**

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 is the most active ketolide presently under development. It is 5 to 10 times more active than telithromycin (Aventis ketolide) against *S. pneumoniae* and *S. pyogenes* including resistant strains. It has equal activity to telithromycin and azithromycin against *H. influenzae*. The increased activity can be attributed increased ribosomal binding. Compared to macrolides that bind only to domain V, ABT-773 binds to both domains II and V. The binding is essentially irreversible and provides bactericidal activity against *S. pneumoniae*.

**Key issues facing the ABT-773 development program are summarized below****QTc Issues**

The potential for QTc prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide. Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies. There is considerable scientific uncertainty in relating the findings from in vitro assays and animal models to clinical risk of malignant arrhythmias. In an effort to gain more

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knowledge these agencies are requiring the pharmaceutical companies to do additional test including

- ICH guidelines require data from animal models and 200 patients
- FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
- FDA has question whether ketolides behave like macrolides
- FDA requested additional dog tox work to evaluate QTc of ABT-773
- ABT-773 studies required including ECG monitoring in pivotal Phase 3 studies.
- FDA may require a Phase I study in patients with underlying cardiac disease, but the design for these studies has not been determined.
- Some antimicrobials now contain warnings for QT prolongation such as moxifloxacin.
- Telithromycin (Ketek) data residing at FDA will be reviewed by FDA Advisory Committee at a meeting scheduled for May 2001 probably related to concerns about efficacy and not related to QTc concerns.

The ketolide ABT-773 will be considered guilty until proven innocent because it is related to erythromycin and clarithromycin which are also suspect and under scrutiny. ABT-773 has the following data related to its potential or lack of potential to affect the QT interval.

- Preclinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose  $\geq 800$  mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

The Venture plan for dealing with the uncertainties related to developing a drug which has an unknown potential for prolonging the QT intervals is to pro-actively attempt to find out as much about our drug and the science related to QTc by;

- Completed preclinical evaluation of ABT-773
- Initiate FDA recommended dog studies.
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Perform FDA requested study of QTc in patients with pre-existing cardiac disease; perform phase I study as required by CPMP.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.

#### Liver Toxicity Issues

The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QTc issues, since both of these problems have resulted in

drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all antimicrobials are under going extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity, scheduled for February 11-12, 2001. Jean Fox will attend this meeting and report back on it so that we will be able to update this topic at the February meeting.

In the Japanese bridging study run in Hawaii we saw increases in LFTs in Japanese subjects. This was very disturbing, since increases in LFTs were seen only in the Japanese subjects. In addition the Japanese subjects had AUCs which were 50% higher than the western subjects. LFTs in over 1000 western subjects did not show any problems. Since, the Japanese subjects with elevated LFTs did not show a dose response, it was felt that the changes in LFTs might be related to the high caloric diet on the unit. To answer this question Phase I food interaction and a repeat of the bridging study was preformed in Japan. The results of this study showed no evidence of any problem with LFTs in the Japanese or Caucasians. Based on the encouraging results we will continue moving forward with the Japan Program.

#### **Phase III Tablet Program**

The Phase III tablet program is underway after several delays related to manufacturing of the 150 mg tablet to replace the 300 mg tablets and the late date (11/27/00) of the FDA End of Phase II meeting. The present plan is to complete the Phase III 150 mg once daily indications in the US and Europe this year. These studies include two pharyngitis studies compared to penicillin 500 mg TID, one ABECB study in the US compared to Azithromycin, and one European ABECB study compared to Levofloxacin. The CAP and sinusitis dose selections studies are running globally, but no European sites are enrolling yet due to the changes in the protocol following the FDA End of Phase II meeting. We are increasing sites and planning to go to the Southern Hemisphere if needed to complete the studies before the start of the fall respiratory season. These changes have added additional costs that will add approximately \$5.0 MM to the budget.

The results of the CAP and Sinusitis studies have the potential of generating divergent development paths based on differences in AI and PPD regulatory and commercial considerations. PPD would prefer to have 150 mg once daily for all indications and AI would prefer 150 mg once daily for pharyngitis and ABECB and 150 mg BID for CAP and sinusitis. Once we complete the study we will need to meet to iron out the possible options.

#### **ABT-773 IV Formulation Program**

The IV formulation program is presently unfunded. The IV program is important to overall program because of the following;

- Hospital formulary acceptance
- XX% share gain in Tab sales due to step-down therapy
- Positions 773 for serious infections
- Support for *S. pneumoniae* resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provide additional information on QTc effects

The ABT-773 IV program received partial funding last year both from PPD and HPD, but has not been funded for 2001. The following outlines the IV program fund and funding needed.

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
  - Formulation development (lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV (\$7MM)
  - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)

The clinical program with 2001 funding decision in February will included;

- |  |         |
|--|---------|
| • Single Dose-rising Phase I study         | Apr/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND                              | Oct/01  |
| • Initiate Phase III                       | Dec/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |

The Venture would recommend funding the Phase I study to determine safety and tolerability profile as a GO/No Go decision. Assuming a GO decision we would need \$7 MM 2001 to start Phase III program.

#### Pediatric Program

The pediatric suspension program is on hold. ABT-773 is 5 to 7 times more bitter than clarithromycin. This will make the development of an acceptable formulation very difficult. The first prototype tested had a taste that was better than clarithromycin but not as good as azithromycin. The pharmacokinetics showed AUCs that were only 70% of the tablet formulation. Even with the difficulties of making an acceptable formulation the pediatric formulation would have benefits including increasing the perception of safety, better pricing and acceptance in European markets, and FDA requires studies in pediatrics. The Venture would recommend continuing the hold until we resolve other issues and then re-evaluate possible ways of overcoming the taste problem.

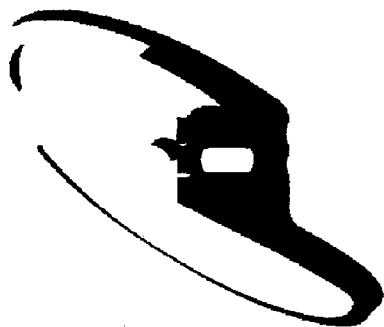
#### **Japan Development Program**

The Japan development program is planned in coordination with Taisho and Dainabot. Taisho funds 10.69% of global development costs and 50% of local Japan costs. The Venture is attempting to use a bridging strategy as the primary plan for development in Japan. The Phase I studies in Japan which were initiated in response to the LFT problems in the first bridging study, have been completed. There were not increases in the LFTs of the Japanese or Caucasians in the study. We will be meeting with Taisho and Dainabot to formulate a plan to present to Kiko in the 2<sup>nd</sup> or 3<sup>rd</sup> Quarter.

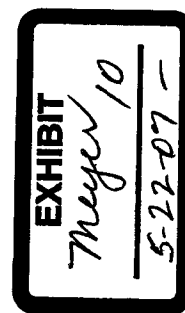


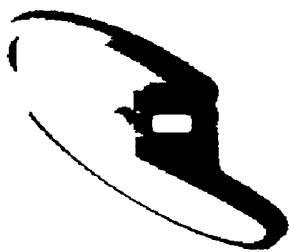
## **Deposition Exhibit 10**

**P's Exhibit IN**



# ABT-773 Update February 12, 2001

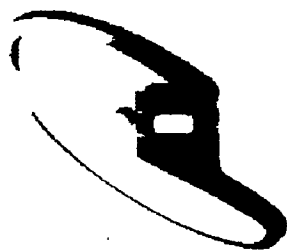




# Agenda

- Introduction
- The molecule
- Phase III tablet program Issues
  - QT
  - Liver Function
  - Dosing
- IV program
- Pediatric program
- Japan program

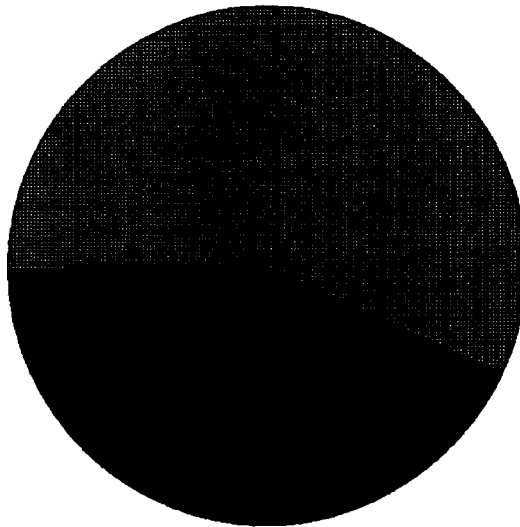
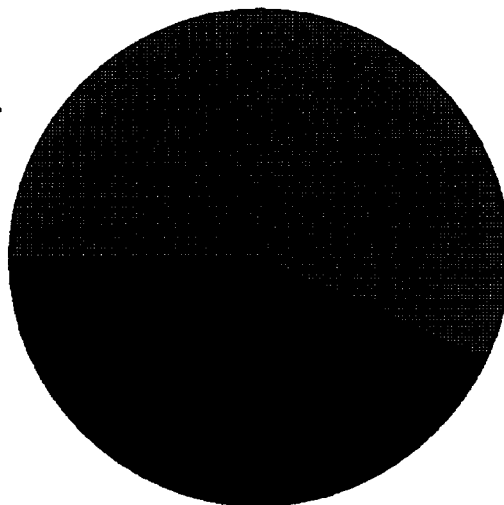




## Global Antibiotic Market Sales Current vs Future Projection

1999 Global Sales \$20.6B

2005 Global Sales \$25.3B



The antibiotic market is a large market and is expected to expand on a global sales basis

# Global Market Drivers

## Negative vs Positive Drivers

- **Antibiotic Resistance**

Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓  
Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

- **Patent Expirations**

May increase price sensitivity and bargaining power of MCOs ↓  
Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↓

- **Unmet Need** ↓

—Overall unmet need relatively low  
—Cost, convenience, tolerability take on added importance  
—Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

- **Competition** ↓

—6 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox  
—Continued discovery/development activity by key competitors  
—High level of promotional activity

Negative driver ↓  
Positive driver ↑

# Key Success Factors

## U.S. vs ex-U.S.

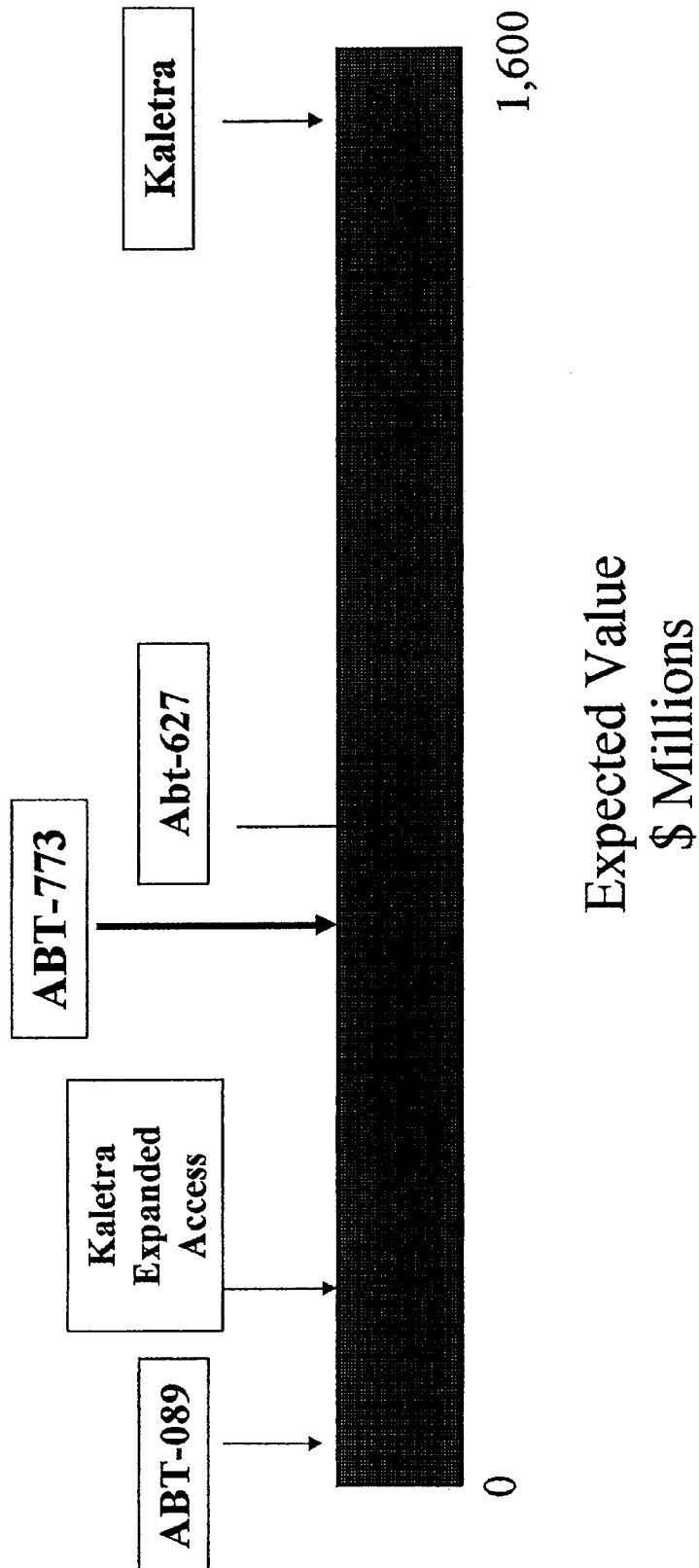
U.S. Assessment		Ex-U.S. Assessment	
Profile	Efficacy	++	Requires a certain baseline level of efficacy across all indications as a "ticket to entry", but is difficult to differentiate agents based on efficacy
	Tolerability	+++	Success of Zithromax and Levaquin have redefined expectations for tolerability of new agents; agents must offer very good tolerability given numerous alternatives
	Convenience	+++	Zithromax and recent quinolones have moved the market toward short course therapies dosed once daily; Biaxin in 1991 represented the last major BID entrant
	Resistance Claim	++	Important to leverage the overall ketolide message, and to maximize formulary access, although availability of data may be able to accomplish same end
	Price	+	Able to set price in accordance with optimal price/demand relationship; only moderate price sensitivity in market, though this could increase with increased number of generic competitors over mid-term
Regulatory	Approvability	+	With data showing equivalence to comparators, is not a major area of concern
Profitability	COGS	+	Allows for > 90% SMM given price parity to Zithromax
	Price	+	Assumes price parity to Zithromax
		+++	While also difficult to differentiate based on efficacy, efficacy takes on added importance with respect to regulatory approval, especially in CAP.
		++	Although important, markets are willing to bear somewhat higher incidence of adverse events, provided they are not severe (i.e. taste perversion); over time, however, AE hurdles will continue to be increased
		++	While in some cases durations are even shorter (azi 3-day AECB), market levies relatively minor penalties for BID dosing
		+++	May prove critical in the regulatory decision of approvability, as well as in setting premium pricing
		+++	Pricing figures heavily into the overall profitability of the compound and is governed by merits of product profile relative to other agents.
		+++	Will take into consideration PK profile in addition to clinical data, which could weaken argument for approval; given the pivotal nature of CAP approval to overall compound viability, regulatory risk is magnified; will require very strong clinical data if 150-mg OD is to be supported
		++	Due to pricing constraints, COGS represents a larger issue; current estimates are 76% SMM at launch rising to 87% peak
		+++	Profile may limit optimal pricing

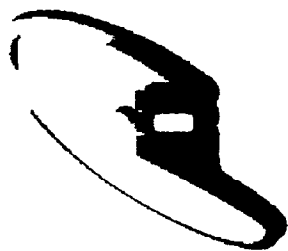
+ Minor Factor

++ Moderate Factor

+++ Major Factor

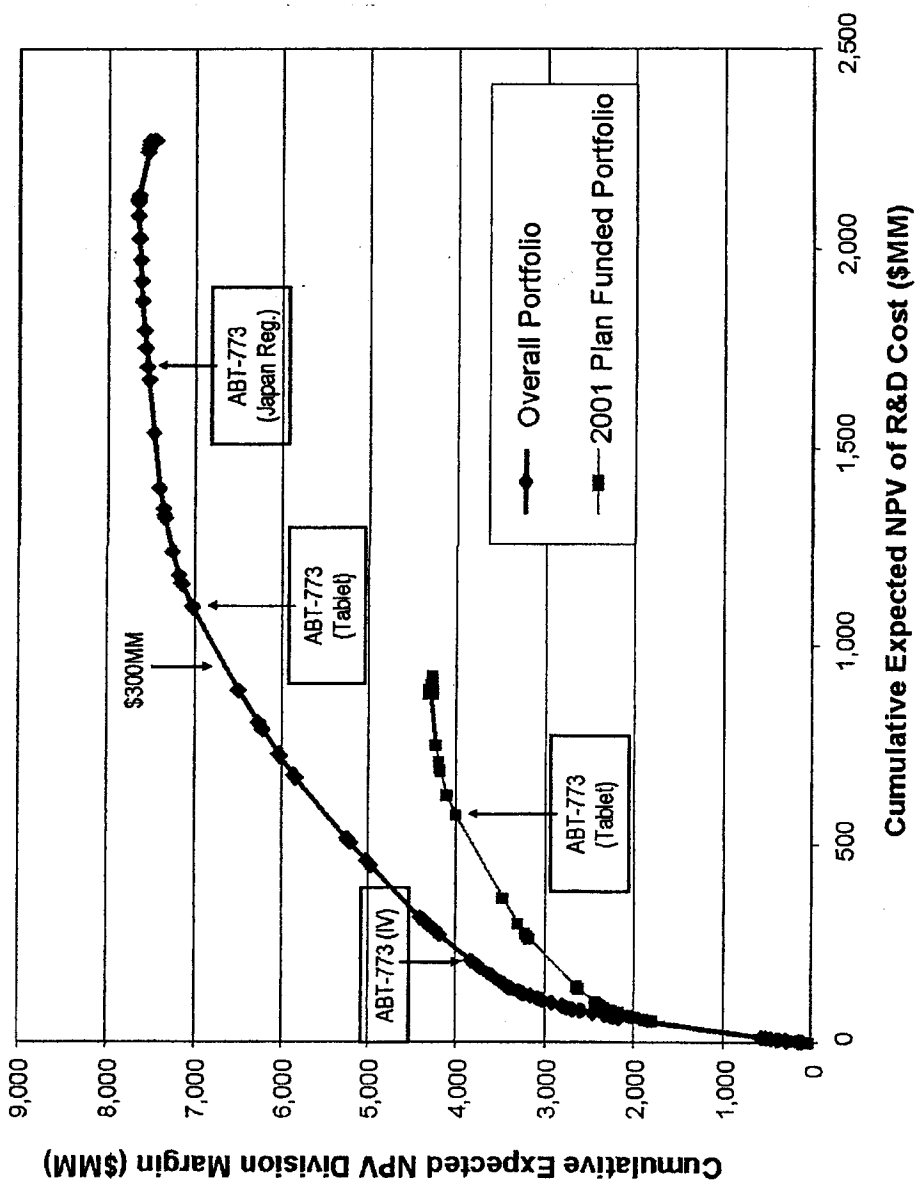
# ***ABT-773 Comparison with other funded projects in 2001 Plan Portfolio***

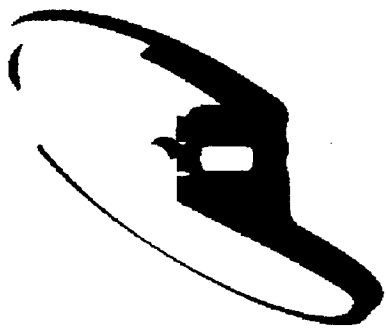




# ***ABT-773 Comparison with other funded projects in 2001 Plan Portfolio***

## **Portfolio Productivity Analysis**

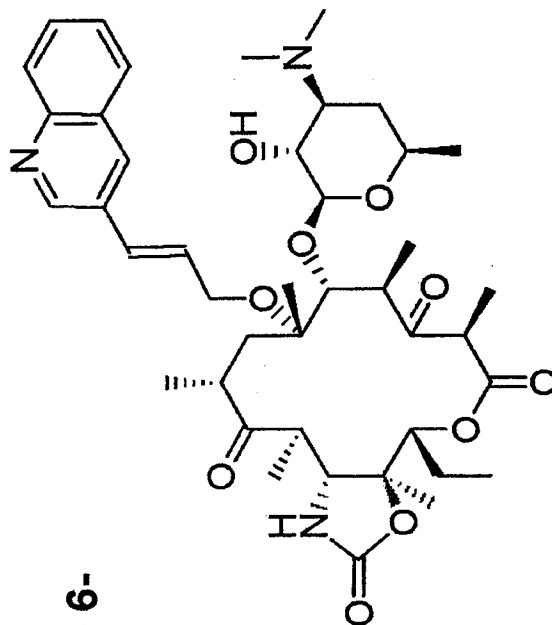




**ABT-773**

**The Molecule**

## ABT-773 Ketolide

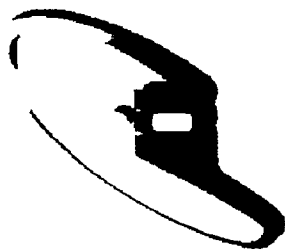


•Quinolylallyl propenyl moiety at the 6-  
0 -position

•Keto group at the 3-position

•Carbamate group at the  
11, 12-position

ABT-773



## **ABT-773 Ketolide**

- **Ketolides are a Novel Class of Antimicrobial**
  - Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development

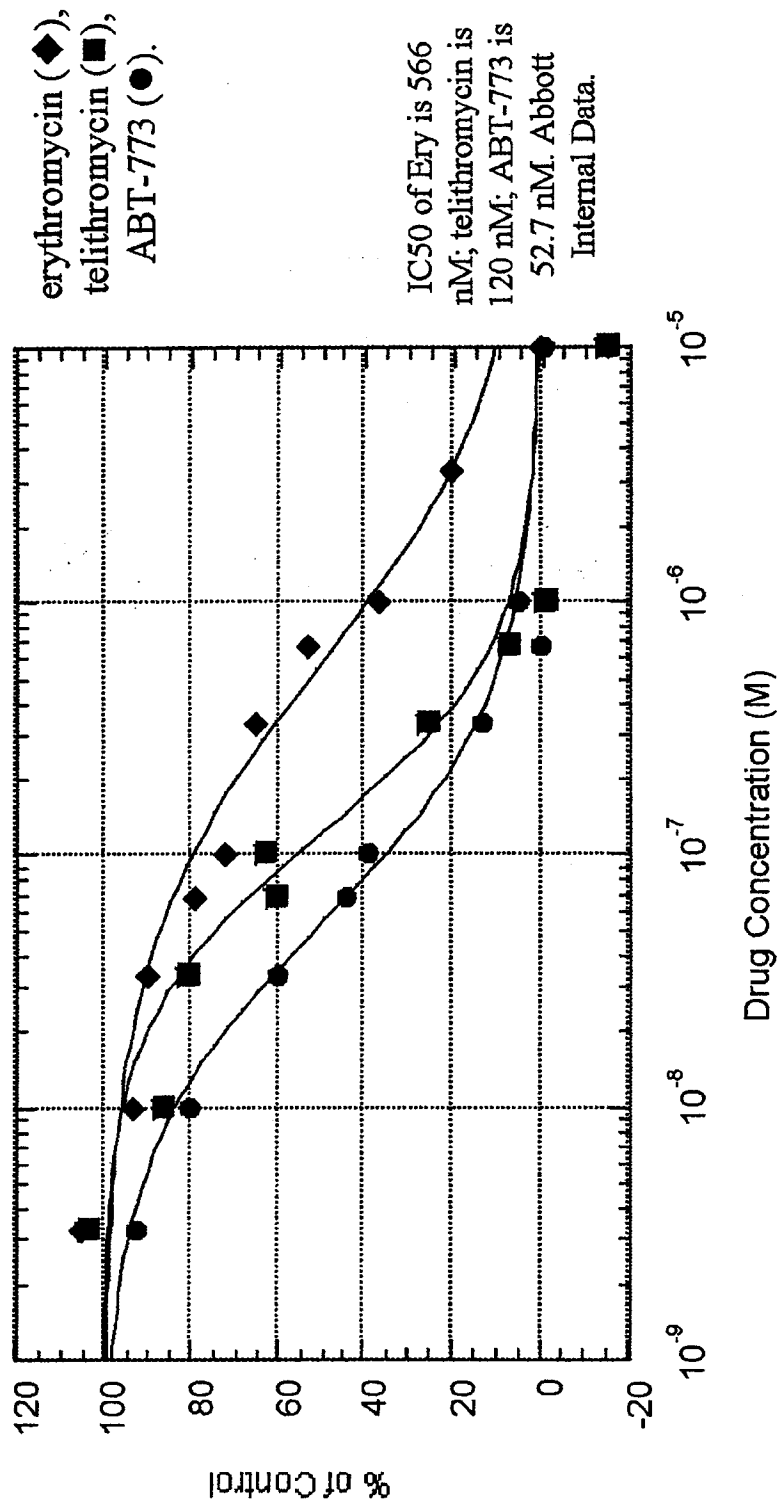


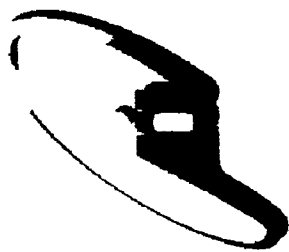
# Microbiology

Organism	MIC <sub>90</sub> $\lambda$ g/ml			
	ABT-773	Ketek	Clari	Azi
<i>S. pneumoniae</i> ery-S	0.008	0.004	0.03	0.12
<i>S. pneumoniae</i> mef	0.12	1.0	4.0	16.0
<i>S. pneumoniae</i> erm	0.01	0.12	>32	>32
<i>S. pyogenes</i> ery-S	0.12	2.0	1.0	2.0
<i>S. pyogenes</i> ery-R	0.5	>8.0	>32	>32
<i>M. catarrhalis</i>	0.25	0.25	0.5	0.25
<i>H. Influenzae</i>	2.0	2.0	16	2.0
Legionella	2.0	2.0	0.06	1.0
<i>M. Pneumoniae</i>	<0.005	<0.005	0.008	<0.005
<i>C. Pneumoniae</i>	0.015	0.06	0.06	0.12

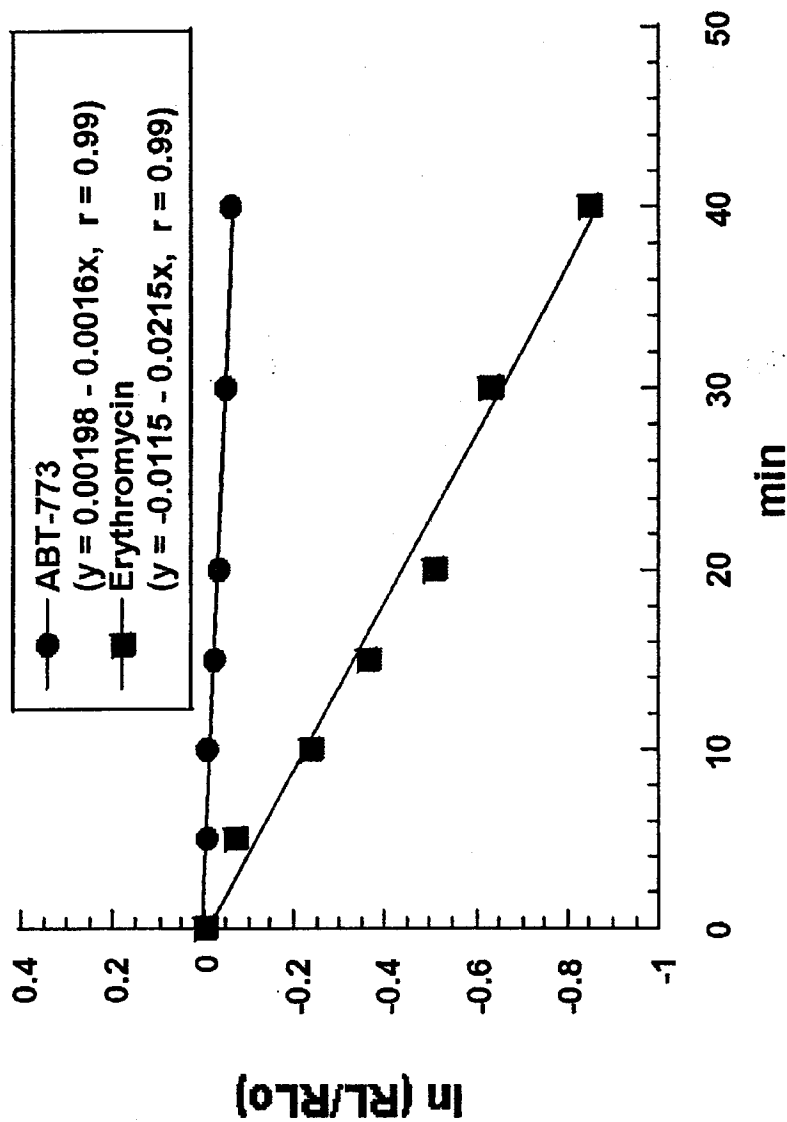


# Ribosome Binding, Susceptible *S. pneumoniae*

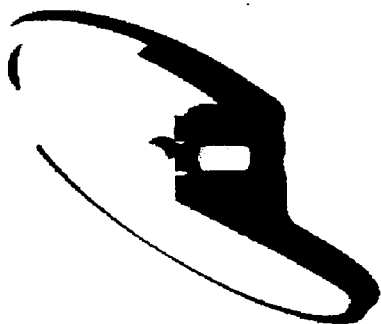




# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.



# QTc potential and Liver Toxicity Issues



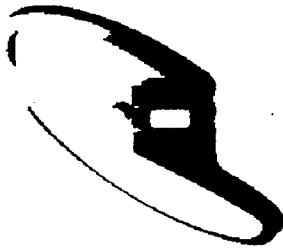
## QTc Prolongation Issues

- Potential for QTc Prolongation is a hot button worldwide
  - Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies
  - ICH guidelines require data from animal models and 200 patients
  - FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
  - FDA has question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QTc
  - Required to include ECG monitoring in pivotal Phase 3 studies
  - FDA may require a Phase I study in patients with underlying cardiac disease
  - Some antimicrobials now contain warnings for QT prolongation
  - Telithromycin (Ketek) data residing at FDA
    - Advisory Meeting rescheduled to May 2001 probably not related to QTc concerns



## **QT<sub>c</sub> Prolongation Issues ABT-773**

- Pre-clinical data positive for QT<sub>c</sub> dose response.
- A possible dose effect in Phase I at total daily dose  $\geq 800$  mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 C<sub>max</sub> 5X)
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)



## **QT<sub>c</sub> Prolongation Issues ABT-773 Plan**

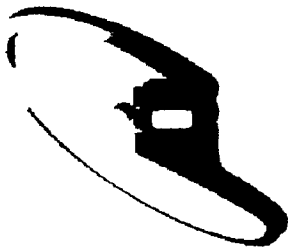
- Completed pre-clinical evaluation of ABT-773
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Planning FDA requested study of QTc in patients with pre-existing cardiac disease.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.





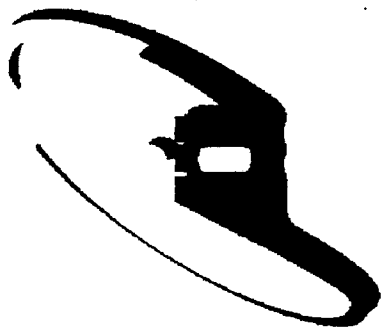
## Liver Toxicity Issues

- Potential for liver toxicity is a concern for the FDA
  - Recent liver toxicity seen with Trovofloxacin are of concern to regulatory agencies.
  - Gemifloxacin recently not approved by FDA because of liver toxicity concerns.
  - FDA meeting on guides to industry on how to study liver function scheduled for February 11-12, 2001



## **Liver Toxicity Issues for ABT-773**

- Preclinical tox showed some effect on the liver function.
- Japanese in bridging study showed increased LFTs.
- No evidence of LFT issue in Western subjects.
- No evidence of dose response.
- Repeat of Japanese bridging study in Japan showed No evidence of LFT increases in Japanese or Caucasians.
- ABT-773 plan for accessing problem
  - Continue to monitor LFT in Phase III programs.
  - Jean Fox will attend FDA meeting.



# Phase III Program

# Phase III Program

## Proposed Indications and Treatment Duration

Infection	Dosage	Duration
Pharyngitis/Tonsillitis due to: <i>S. pyogenes</i> *	150 mg QD	5 d
Acute bacterial sinusitis due to: <i>H. influenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i> **	150 mg QD or BID 150 mg QD or BID 150 mg QD or BID	10 d 10 d 10 d
Acute bacterial exacerbation of chronic bronchitis due to: <i>H. influenzae</i> <i>H. parainfluenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i> **	150 mg 150 mg 150 mg 150 mg	5 d 5 d 5 d 5 d
Community-acquired pneumonia due to: <i>C. pneumoniae</i> <i>H. influenzae</i> <i>L. pneumophila</i> <i>M. pneumoniae</i> <i>S. pneumoniae</i> **	150 mg QD or BID 150 mg QD or BID 150 mg QD or BID 150 mg QD or BID 150 mg QD or BID	10 d 10 d 10 d 10 d 10 d

\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.

## Phase III Program Studies Started in Year 2000

Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	185/520	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	0/520	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	131/600	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	0/500	EU (Non-IND)



## **Phase III Program Studies Started in Year 2000, Con't**

### **Dose Finding Studies for Sinusitis/CAP:**

<b>Study</b>	<b>Indication</b>	<b>ABT-773 Regimen</b>	<b>Comparator</b>	<b>Number Subjects</b>	<b>Location</b>
<b>M00-225</b>	<b>Sinusitis</b>	<b>150 mg QD vs. 150 mg BID 10 days</b>	<b>None</b>	<b>137/500</b>	<b>US, EU (IND)</b>
<b>M00-219</b>	<b>CAP</b>	<b>150 mg QD vs. 150 mg BID 10 days</b>	<b>None</b>	<b>76/500</b>	<b>US, Canada, EU (IND)</b>

# SDG Analysis of Ph. III CAP Development Options

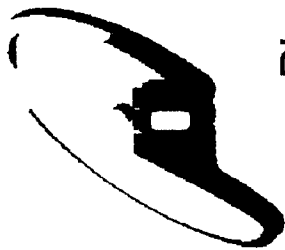
CAP Development Strategy	Timeline Impact	Incremental Cost	Relative Regulatory Risk	Potential for 150 mg. QD in CAP
1. 150 mg QD only Ph. III (Begin now)	8/2002	0		Yes
2. Further Phase II 150x dose ranging, then Phase III		\$5.4M	Low	Yes
3. Parallel Phase III program for 150 mg QD/150 mg BID			Low	Yes
4. 150 mg BID only Ph. III (Begin now)	8/2002	0	Mod	
5. 300 mg QD only Ph. III (Begin now)	8/2002	0	Low	
6. Phase III open-label dose ranging	8/2002	\$7.2M	Low	Yes

Selected Strategy

Positive Factor

Neutral Factor

Negative Factor



## Dosing Issue

### 150 mg BID vs 150 mg QD: Background

- Phase II data indicated 300 mg QD was not viable due to high levels of diarrhea (10-20%) and taste perversion (10-20%)
- Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD
  - 150 mg QD currently being evaluated in ongoing phase III trials in these indications
- Dosing selection for CAP and sinusitis confounded by limited data
  - few bacterial isolates, particularly with H. flu, in sinusitis
  - no 150 mg arm in CAP trial
- To increase probability of correct dose selection in CAP/sinusitis, additional studies are ongoing to generate more data in these indications
  - 150 mg QD vs 150 mg BID CAP & sinusitis trials ongoing

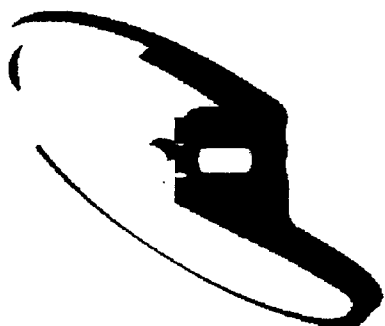




# Dosing Issue

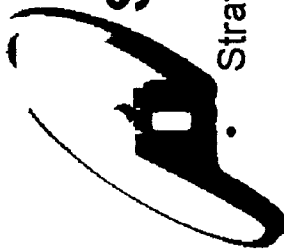
## 150 mg BID vs 150 mg QD: Implications of Decision

- Regulatory and commercial environments differ dramatically between U.S. and ex-U.S.
  - For U.S., market:
    - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
    - Approval on indication-by-indication basis
    - Optimal strategy for U.S. may be to pursue QD dosing for CAP/sinusitis
  - For ex-U.S. market:
    - CAP data represents the “lynchpin” for approvability of the entire molecule, hence a conservative BID approach may result in lower regulatory/commercial risk
    - Relatively minor commercial impact of BID dosing
    - Optimal strategy for ex-U.S. may be to pursue BID dosing for CAP and perhaps sinusitis
- A decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01
  - Data may not show a clear “winner” due to relatively low power of studies; may be a difficult decision
  - Due to soft global flu season and protocol amendments, enrollment is behind plan and could impact timing of decision
- A plan to have divergent US/Ex-US clinical programs in CAP/sinusitis may be required to minimize regulatory / commercial risks
  - Cost / timeline implications



# ABT-773 IV Program





## ABT-773 IV Formulation Strategic, Commercial, and Technical Value

### Strategic Value

- IV represents a channel not currently served by Anti-infective Franchise
- Leverages presence of Medical Center Reps and experience with ID community

### Commercial Value

- IV availability figures favorably into decisions regarding formulary access to molecule
  - potential advantage over telithromycin, which will not have an IV
  - required to compete effectively with Zithromax, Tequin, Avelox which have IVs
- Positive impact on tablet formulation
  - estimated \$36MM incremental to peak tablet sales due to step-down therapy
  - Enhances overall “potency” image of brand

### Technical Value

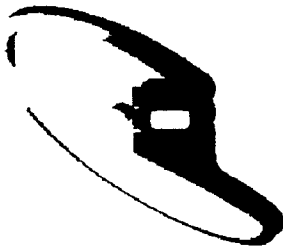
- Support for *S. pneumoniae* Resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provides additional information on QT effects

IV launch currently lags tablet launch by 1 year; any further delays will reduce the potential value



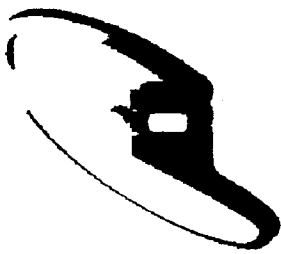
## **ABT-773 IV Program Formulation Objectives**

- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counter ion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.



## **ABT-773 IV Formulation PPD/HPD Funding Status**

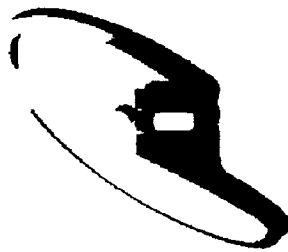
- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV (\$7MM)
  - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)



## **ABT-773 IV Formulation**

### ***Animal Pain Study Results***

- Assessed 6 prototypes (3 different counter ions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
  - Results not conclusive
  - Need to evaluate in humans
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.



## **ABT-773 IV Planned Clinical Program**

*With 2001 funding decision in Feb:*

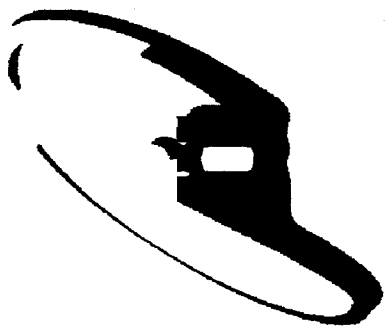
- |  |         |
|--|---------|
| • Single Dose-rising Phase I study         | Apr/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND                              | Oct/01  |
| • Initiate Phase III                       | Dec/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |



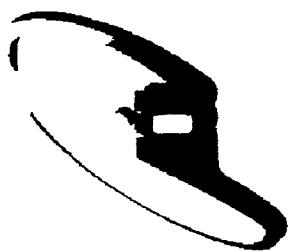
## ABT 773 IV Program Summary

- **Comments**

- Funding for '01 not available PPD/HPD
- Go/No go could be made after Phase I based on safety profile (pain, QT, GI)
- Milestone funding recommended (\$1MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant *S. pneumo* claim
- Total Program Cost 2000-2003 (\$22.5MM)



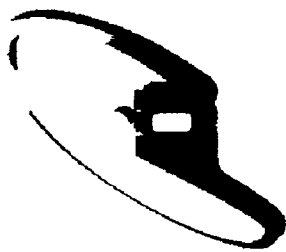
# Pediatric Program



## **ABT-773 Pediatric Formulation**

### **Importance to the 773 program**

- Increased perception of safety
- Better pricing and acceptance in European markets
- FDA requires studies in pediatrics



## **ABT-773 Pediatric Program Formulation Objectives**

- Develop coated particle formulae for global use
  - coated particles for Suspension - 150mg/5mL & 300mg/5mL
  - coated particles as a dry syrup, sprinkle or sachet.
- Desired Properties
  - Once a Day Dosing
  - Acceptable 'Initial Taste'
  - Minimal 'After Taste'
  - No Unpleasant Mouth-feel
  - Acceptable Color and Flavor
  - No Refrigeration Required.

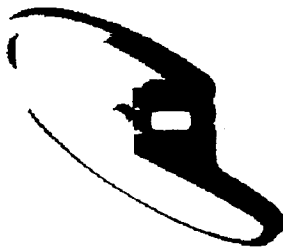
# ABT 773 Pediatric Program Taste Assessment

## Sensory Analysis of Uncoated Drugs Summary of Results

The three drug substances can be ranked from most to least bitter as follows:

Drug Substance	Concentration (mg/mL) Exhibits an Initial Bitter Intensity (on a 1-10 scale)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

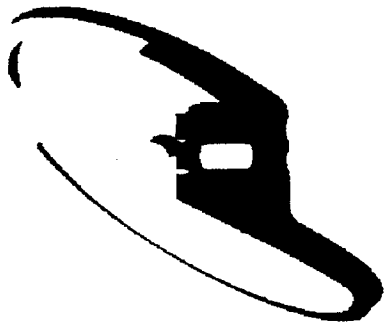
- ABT-773 is approximately five times more bitter than clarithromycin



## **ABT 773 Pediatric Program**

### ***Taste Assessment***

- The ABT-773 encapsulated prototype #2 may be at risk of dosing compliance problems due to flavor quality.
- Overall ABT-773 Prototype 2
  - Less bitter than Biaxin both initial and after taste
  - More bitter than Zithromax both initial and after taste
- For ABT-773 Prototype 2, the flavoring aromatics and sweetness decay quickly, exposing the bitterness which lingers throughout the aftertaste at or above the “concern” intensity level.



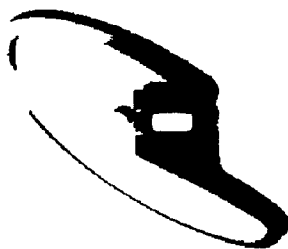
# Japan Program



## **Japan Program Taisho**

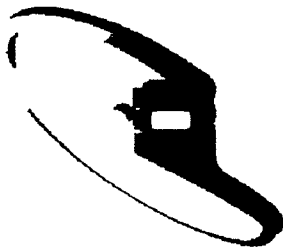
- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan





## Japan Program Clinical Plan

	<u>Start</u>
<ul style="list-style-type: none"><li>• Phase I in Japan<ul style="list-style-type: none"><li>– Food Effect Study</li><li>– Single and multiple dose study</li><li>– Review data (Abbott/Taisho)<ul style="list-style-type: none"><li>• PK data Japanese vs Caucasian</li><li>• Development program strategy</li></ul></li><li>– Present Kiko data and recommend development program May/01</li><li>– Start Tissue Conc. Study</li></ul></li></ul>	<div>Completed</div> <div>Completed</div> <div>April/01</div> <div>2Q/01</div>



## **Japan Program Clinical Plan**

- PK similar in Japanese and Caucasians (12/02 filing)
  - Recommend to Kiko same dose in Japan as in ex-Japan
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in skin infections, dentistry, otolaryngology, UTI and pan-bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians (12/03 filing)
  - Phase II dose ranging study in CAP (Bridging study)
  - Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing



# **Deposition Exhibit 11**

## **P's Exhibit IR**

Eugene X  
Sun/LAKE/PPRD/ABBOTT  
02/22/2001 06:57 PM

To Stan Bukofzer/LAKE/AI/ABBOTT@ABBOTT  
cc  
bcc  
Subject 773.material

Stan,  
here are some background materials



ABT-773 Development Plan 1.doc



Leiden review Dec00.ppt



End of Phase 2 Meeting Minutes.doc



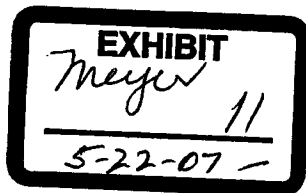
End of Phase 2 Meeting - Primary Slides.ppt



ABT773 Review Pharma Exe Meeting.rtf



ABT-773 Pharma Exe Meeting.ppt



Confidential

ABBT204959

**ABT-773**  
**DEVELOPMENT PLAN**

C. Meyer [DATE]

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## A. Executive Summary

## A.1 SWOT Analysis

Table A.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<p>ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Erm AM and Mef phenotypes; it has not been shown to induce MLS<sub>S</sub> (macrolides, lincosamides and streptogramin B) resistance.</p> <p>The in vitro microbiological profile of ABT-773 shows a 4-fold superiority to telithromycin which should translate into 3 to 5 times lower daily dose than the first ketolide.</p>	<p>Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.</p> <p>Capitalize on micro superiority and lower dose by generating comparative efficacy/safety data in Phase IIIb studies.</p>
Weaknesses	<p>Pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged.</p> <p>In Phase IIb studies, 300 mg QD has higher GI/Taste perversion adverse events compared to clari 500 mg BID</p> <p>The Phase III clinical program is large, intense, and must be conducted successfully in a relatively short period of time. There is also very stiff competition from other major pharmaceutical companies to enroll patients. Many of these companies are paying inflated grants fees and have simpler Phase IV protocols that will entice investigators.</p> <p>An IV and pediatric formulation will not be available at launch. An IV formulation would further enable us to position this product as an effective drug for a range of mild to severe infections. A pediatric formulation would further underscore the safety properties of the product. Both formulations would promote improved acceptance of this product.</p>	<p>Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure.</p> <p>Monitor enrollment closely and be proactive with CROs in opening additional sites and offering appropriate incentives to push enrollment. Prepare to open sites in the Southern hemisphere.</p> <p>HPD has identified initial funding this year to bring an IV prototype into Phase I studies. Further development funding has been requested in 2001 in the HPD plan and has been included in a PPD blue plan request.</p> <p>Present initial pediatric Phase I data as well as taste evaluation will be available mid-October for management decision on future funding.</p>
Opportunities	<p>ABT-773 has the potential to be able to address competition with azithromycin with short course therapy for mild infections, as well as quinolones for more serious infections. Resistance (PRSP/MRSP) is a growing concern and will be a major consideration when this product is introduced.</p>	<p>Conduct appropriate comparative Phase III studies to get approval for all the RTI indications, both in U.S. and European countries. Collect enough resistant isolates to obtain the claim for resistant <i>S. pneumoniae</i>.</p>

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	<p>If 150mg QD is proven effective, COGs for this product will be within a very acceptable range for obtaining a high profit margin in all markets.</p> <p>Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i>.</p>	<p>Continue to improve throughput and yield and introduce appropriate process improvements in SPD to further bring down the bulk drug costs. Propose intermediate step 5 as the starting material for the bulk drug to enable further process improvements post-filing.</p> <p>This opportunity exists for the FDA labeling only and recent information indicates that FDA is rethinking their position on granting this separate claim. Other antibiotics have been granted this claim with as little as 15 isolates.</p>
Threats	<p>Current data available is insufficient to predict that 150mg QD will be effective in more serious indications of CAP and Sinusitis. Current two dose studies are being carried out in 150mg QD and 150mg BID to assess the potential of 150mg BID being the required dose for these indications.</p> <p>Regulatory uncertainties over how to deal with ketolide/macrolide class</p> <p>Elevated liver enzymes were seen in a small number of Japanese volunteers in a PK study.</p> <p>The Japanese development program has been delayed due to findings in the first Japanese PK study indicating a significant difference in the PK profiles between Japanese and non-Japanese subjects. Timing, dose selection and funding for the Japanese program is unknown at this time.</p>	<p>May need to market 150mg QD for mild infections and 150mg BID for more severe infections.</p> <p>ABT-773 is similar to clarithromycin and erythromycin in its effect on QT intervals in preclinical studies. Current clinical data indicates no evidence of QTc prolongation. BCG monitoring is included in all the Phase III studies. An HPD funded phase I study of an IV formulation prototype will provide additional information on QTc prolongation.</p> <p>Current expert analysis has concluded that there no clinically significant interaction. The study is being repeated in Japan to further evaluate.</p> <p>Repeat Japanese PK study in Japan along with a food effect study. Once results are available, meet with clinical advisory committee KIKO and determine the development requirements for Japan.</p>

## A.2 Development Plan Summary

Considering the rapid and extensive emergence of penicillin and macrolide resistant *S. pneumoniae*, and the remaining patent life of Clarithromycin, the flagship of Abbott's pharmaceutical product line, ABT-773 was approved by PPCC in 03/97 as a candidate for Development by the Anti-Infective Venture. The mission of the Venture is to develop ABT-773

as a first line therapy in community acquired lower and upper respiratory infections (RTIs).

The proposed indications and treatment durations below position this product to compete effectively in the RTI arena both in the U.S. and in international markets. These are the required indications to be considered as first line therapy for RTIs.

- |  |         |
|--|---------|
| • Community-Acquired Pneumonia                       | 10 Days |
| • Acute Bacterial Sinusitis                          | 10 Days |
| • Acute Bacterial Exacerbation of Chronic Bronchitis | 5 Days  |
| • Acute Streptococcal Pharyngitis/Tonsillitis        | 5 Days  |

Our goal is to provide the physician with an agent which will have the safety and tolerability of azithromycin for mild to moderate infections but with the strengths of the quinolones for moderate to severe infection of the respiratory tract particularly for (PRSP/MSRP) resistant *S. pneumoniae*.

We will also be seeking additional labeling to include the treatment of macrolide-resistant *Streptococcus pneumoniae*, penicillin-resistant *Streptococcus pneumoniae*, and atypical pathogens to include *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* in the above-mentioned indications. Susceptibility and clinical treatment trial data for macrolide-resistant *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae* will be provided from Phase 3 trials. A request for appropriate breakpoints to include these strains will also be provided in the NDA.

**B. Marketplace****B.1 Marketplace SWOT Analysis**

<b>Table B.1a SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)</b>		
<b>CATEGORY</b>	<b>ITEM (Probability/Impact)</b>	<b>STRATEGY</b>
<b>Strengths</b>	Large market in terms of both prescriptions and sales	None
	Emerging international markets may contribute to positive market growth ex-U.S. Antibiotic resistance ultimately renders older agents obsolete, allowing newer agents access to the market	Move forward with global development program Target resistance claim for ABT-773
<b>Weaknesses</b>	May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance	Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS)
	Difficult to differentiate antibiotics High hurdle rate for new agents in terms of convenience and adverse event profile High level of promotional support required to reach optimal sales levels	Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy Evaluate ABT-773 profile upon receipt of phase III data Build adequate promo levels into LRP
<b>Opportunities</b>	ABT-773 represents a hedge against Biaxin IR patent expiration in 2005	Evaluate optimal portfolio/promo strategy between Biaxin XL and 773 in light of patent expiration
	Potential for I.V. formulation, expands scope of franchise into new market segment Potential for pediatric formulation	Continued funding of IV program Make go/no-go decision based on taste/PK data
<b>Threats</b>	Telithromycin launch 2-1/2 years in advance of ABT-773	Monitor launch of telithromycin, adjust 773 strategy if necessary based on market feedback
	Considerable number of antibiotics lose patent exclusivity by 2005-may put negative price pressure on market May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance New entrants	Work with managed care group to evaluate potential impact Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS) Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy

## B.2 Epidemiology/Disease Class

Respiratory tract infections represent the majority of community-acquired infections. Causative pathogens for these infections are most often *Strep. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *M. pneumoniae*. Table X summarizes the annual incidence of community-acquired respiratory infections.

Table B.2.1: Annual Incidence of Community-Acquired Infections

	Infection	Annual Incidence (U.S., millions)	Annual Incidence (Ex-U.S., millions)
Upper Respiratory	Sinusitis	37	94
	Otitis	18	46
	Pharyngitis	12	30
Lower Respiratory	Bronchitis	14	36
	Pneumonia	4	10

## B.3 Market Overview

### U.S. Market

1999 U.S. antibiotic prescription and sales data are presented in the table below.

			1995	1996	1997	1998	1999	CAGR <sub>95-99</sub>
U.S.	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

The macrolide class has grown significantly over recent years, from \$771MM in 1995 to \$1,596MM in 1999, though most of this growth (\$673MM) was due to gains in Zithromax, underscoring the importance of convenience, adverse event profile, and price in this market.

**Ex-US Market**

The ex-US antibiotic market had sales of \$11.6B in 1999, an increase of approximately 5.9% over 1998; however the CAGR over the past 3 years has been only 0.7%. Antibiotic usage is expected to decline 1-2% per year in the largest, most developed AI regions – Europe, Japan and Canada; however, Latin America and PAA are expected to show 1.5% - 3.0% growth as access to healthcare continues to improve. Standard units (used as a proxy to normalize units across regions) have decreased approximately 1.7% versus prior year, despite strong sales growth. This reflects a gradual shift to newer, premium priced agents, particularly in less developed regions.

Clarithromycin performance in AI markets continues to be strong, out-performing azithromycin sales and growth rate by almost 3 to 1. Although the ex-US quinolone class market share (15.3%) significantly lags US performance (28.4%), the quinolones show strong growth, fueled in part by new product introductions such as levofloxacin. It should be noted, however that almost 80% of Levo sales are in Japan, where sales increased 40% over the previous year. Levo launched in 1994 in Japan, but has only recently been introduced in other ex-US markets. Moxifloxacin was launched Q4 1999 in Germany, and has begun roll-out to other European markets in 2000. Moxi has not yet been submitted in Japan. Gatifloxacin approval is expected for European markets in Q2 2001, and is currently in Ph III for Japan. Cephalosporins continue to dominate the ex-US market, with sales share of over 40% (compared to only 17% in the US).

**Table B 3.b Ex-US Sales**

	1999 Sales			1999 Standard units		
	Sales (\$000s)	Share	Growth (99/98)	SU (000s)	Share	Growth (99/98)
<b>Penicillins</b>	\$2,475	21.2%	0.8%	NA	NA	NA
Augmentin	\$684	5.9%	1.9%	1,213	6.4%	2.0%
Amoxicillin	\$684	5.9%	-8.1%	3,479	18.3%	-1.9%
<b>Cephalosporins</b>	\$4,948	42.3%	7.5%	NA	NA	NA
Cefaclor (Ceclor)	\$344	2.9%	-8.0%	638	3.4%	-8.9%
Cef. Axetil (Ceftin)	\$288	2.5%	2.9%	261	1.4%	2.7%
Cef. Proxetil (Vantin)	\$185	1.6%	7.0%	186	1.0%	3.9%
<b>Ext. Spec. Macrolides</b>	\$2,257	19.3%	5.1%	NA	NA	NA
Clarithromycin	\$904	7.7%	12.0%	816	4.3%	8.3%
Azithromycin	\$344	2.9%	4.1%	113	0.6%	4.6%
Roxithromycin	\$253	2.2%	0.1%	257	1.4%	-0.8%
<b>Quinolones</b>	\$1,788	15.3%	11.1%	NA	NA	NA
Ciprofloxacin	\$530	4.5%	1.2%	404	2.1%	4.7%
Levofloxacin	\$467	4.0%	54.0%	248	1.3%	31.2%
<b>TOTAL</b>	<b>\$11,685</b>	<b>100%</b>	<b>5.9%</b>	<b>19,031</b>	<b>100%</b>	<b>-1.7%</b>

Source: IMS retail pharmacy data for all formulations, all audited ex-US markets; standard units used as a proxy for prescription market share, since Rx's are not audited in most ex-US markets

**B.4 Current Treatment Options**

<b>Class</b>	<b>Mechanism of Action</b>	<b>Comments</b>
Penicillins	Cell wall synthesis inhibitor	Mostly generic, class has seen significant decrease as a result of penicillin resistance
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications
Sulfonamides	Folic acid synthesis	Generic agents, relatively high levels of resistance but are still useful in some indications
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; H. flu activity continues to be class weakness, along with GI events, drug-drug interactions, & taste perversion
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram- profile and potential safety issues will be used primarily in nosocomial setting



## B.5 Competitive Analysis – Emerging Competition

Table B.5a Pipeline					
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment
Ketek (telikaromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market.
Pactive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est. launch 12/00	US	Superior to other quinolones for MRSA; highly potent vs. RTI pathogens H. flu, M. cat, and S. pneumo and UTI pathogens E. coli and P. mirabilis, CRSP; potency > spar, trov, grep and ≥ moxi; activity vs. P. aeruginosa?; good atypical and mycoplasma coverage; intracellular penetration; low photo/CNS tox; 700 patient database
Stafloracin	Daiichi Seiyaku	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Potent against MRSA, pseudomonas and bacteroides activity; diarrhea, ALT, low WBC, phototox issues; will likely target severe rather than community infections
Ecenofloxacin	Chiel Foods	Quinolone	II Est. launch 2002	UK	Active against UTI and RTI pathogens; superior to lome and oflo vs. P. aeruginosa. T <sub>1/2</sub> = 14-19 hr; will likely be target to severe rather than community infections
CS-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G+/-; excellent activity against H. flu, c. jejuni, M. pneumo, and C. trachomatis; greater potency than cipro; t <sub>1/2</sub> ~7 hr; BA~80%
T-3811	Toyama/BMS	Quinolone	I Est. launch 2005	Japan	Excellent potency and low toxicity
ABT-492	Abbott	Quinolone	Pre-clin Est. launch 2005	US	Excellent potency, good anti-pseudomonal activity. To initiate phase I 11/00
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est. launch 2006	Japan	Low toxicity; in vitro potency ≥ trov, STFX & HSR-903

**B.6 Unmet Needs**

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation. Table B.6a shows the impact of the pipeline on current unmet market needs.

<i>Table B.6a Unmet Market Needs and the Impact of the Pipeline</i>	
<i>Unmet Need</i>	<i>Pipeline Impact</i>
Activity against resistant organisms	Strep. pneumo, MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant Strep. pneumo strains; quinolone-resistant Strep. pneumo may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gatifloxacin claims 8-methoxy functional group results in lower propensity for resistance development
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (ABCB)
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety profile should be regarded as a necessary component rather than a differentiating one
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market

## C. Product Positioning

### C.1 Product Positioning Options

Positioning Alternative	Strategy	Strengths	Weaknesses
Macrolide replacement	Convert existing macrolide business (including Biaxin) to ABT-773. Desirable if Biaxin XL erosion is expected to be high upon launch of IR generics	<p>Relatively simple strategy to implement &amp; communicate to market</p> <p>Large Zithromax business to target</p> <p>Strategy is a natural extension of 773's activity against macrolide-resistant <i>S. pneumoniae</i></p>	<p>Sales are at expense of Biaxin</p> <p>Will need to achieve a very good tolerability &amp; convenience profile to maximize this strategy</p> <p>May be difficult to keep business from shifting toward generic clarithromycin</p>
Second line (macrolide-sparing)	Co-position Biaxin and ABT-773. Desirable if Biaxin XL erosion is expected to be low upon launch of IR generics	<p>Sales of 773 would be at least partially additive to Biaxin</p> <p>Support of both Biaxin and 773 may allow a broader scope of the RTI market to be served</p> <p>Allows for greater flexibility with price, potential for advantageous price/volume scenarios</p>	<p>Can be difficult to segment &amp; communicate to reps/physicians</p>
Quinolone fighter	Position as a potent alternative to quinolones for RTIs	<p>RTI-specific spectrum of 773 could play well if quinolone resistance develops</p> <p>RTI-specific spectrum of 773 is consistent with "appropriate use"</p> <p>Quinolones are fast-growing market segment</p>	<p>May be difficult to convince physicians that 773 is as potent</p> <p>H. flu activity of 773 is inferior to quinolones</p>

## C.2 Target Product Profile

### C.2.1 ABT-773 Target Product Profile

Table C.2.1 outlines the desired target product profile for ABT-773

Product Profile				
Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Activity against Gram +, Gram -, atypicals	3/1997	High	Confirmed	High
Activity against <i>H. influenzae</i> = azi	3/1997	High	Confirmed	High
Active against 80% of Gram + resistant strains of efflux and MLS-c	3/1997	High	Confirmed	High
Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	3/1997	High	Confirmed	High
Incidence of GI side effects=azi	3/1997	Low	Not Met	High
Incidence of drug-interactions = clari, no contraindications	3/1997	High	6/2001	Medium
QD dosing adult/tablet	3/1997	Medium	6/2001	High
QD dosing ped OS	3/1997	Medium	9/2000	Medium
QD dosing for IV	3/1997	Medium	12/2000	High
Comparable pain at injection site than azi		Medium	12/2000	Low
Less metallic taste than clari XL	3/1997	Medium	6/2001	High
OS equal in taste to Azi, Omnicef		Low	9/2000	High
5-day therapy for most indications	3/1997	Low	6/2000	High
COGS > 80% SMM at launch	3/1997	High	12/2001	Low
Maintain balanced plasma/tissue levels similar to clari		Medium	12/2001	Medium

\* Probability Key:

High = 70-100%

Medium = 30-69%

Low = 0-29%

Table C.2.2 outlines the product profile strengths, weaknesses, opportunities and threats.

Table C.2.2 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<p>Macrolides/ketolides are regarded as an "appropriate" choice for RTIs; could be used to advantage should quinolone resistance develop</p> <p>ABT-773 is generally regarded as more potent than telithromycin and macrolides against Gram-positive causative RTI pathogens, including resistant pathogens</p> <p>ABT-773 may offer unique mechanistic advantages relative to telithromycin and macrolides (ribosome binding)</p>	<p>Leverage recent guidelines to develop support for class in RTIs; monitor quinolone resistance surveillance</p> <p>Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin and other agents via advisory panels, symposia, etc.</p> <p>Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin via advisory panels, symposia, etc.</p>
Weaknesses	<p>Potential for perceived weakness of product with respect to PK profile at 150 mg dose</p> <p>H. flu microbiological activity inferior to quinolones</p> <p>Phase II data suggests moderate levels of diarrhea and taste perversion</p>	<p>Identify strategy to "explain" clinical data in light of PK issues; "ribosome story"</p> <p>May be able to mitigate if clinical eradication data is strong; re-evaluate after receipt of phase III data</p> <p>Telithromycin appears to have even higher diarrhea rate; consider phase IIIb/IV comparative study</p>
Opportunities	<p>Potential for I.V. formulation, has positive impact on image of tablet</p> <p>Potential for pediatric formulation, has positive impact on image of tablet</p>	<p>Continued funding of IV program</p> <p>Make go/no-go decision based on taste/PK data</p>
Threats	<p>May be BID dosing for CAP and/or sinusitis-all recent antibiotics have QD dosing for all indications</p> <p>H. flu eradication may be sub-standard at 150 mg dose</p> <p>Telithromycin may gain 5-day indication for sinusitis-no other antibiotics have 5-day claim</p> <p>Requisite number of resistant isolates for claim may not be achievable for NDA; may require additional trials</p>	<p>Proceed with dose ranging phase III to determine if QD dosing is adequate for these indications</p> <p>Evaluate in light of phase IIIa data (2Q01)</p> <p>In light of phase IIIa data, evaluate whether 5-d vs 10-d ABT-773 arm could be added to gain 5-day indication</p> <p>Evaluate situation at completion of phase III clinical program</p>

**C.2.2 Target Product Label - See Appendix 1**

**C.3 Reimbursement/Pricing Strategies**

**C.3.1 Reimbursement/Managed Care**

Development of reimbursement strategies will be initiated upon completion of the phase IIIa studies, at which time product dosing will have been determined and more certainty to efficacy/AE rates will have been obtained.

**C.3.2 Pricing Strategy**

- a) U.S pricing for 5 days of ABT-773 will be at parity with 5 days of Zithromax, allowing ABT-773 to effectively compete for Zithromax business.
- b) Pricing in most European markets will be set by the government, and will be somewhat dependent on how the ketolide is classified – as a macrolide or as a new class that merits a price premium vs. the macrolide class. Although a price premium would increase revenue per unit, it could potentially limit market penetration, and therefore, reduce total revenue opportunity. Clari will be subject to downward pricing pressure due to European and Japanese price control measures and to generic incursion in LA and PAA markets over the next few years. Therefore, the base case pricing assumption is that ABT-773 will achieve pricing comparable to current clari price per course of therapy.

**C.4 Sales Forecast(s) for ABT-773****C.4.1 U.S. Sales Forecast**

The U.S. forecast is shown in Table C.4.1a, below:

Table C.4.1a U.S. Forecast (Date of Forecast: 7/00)					
	2004	2005	2006	2007	2008
Market (MM TRX)*	195	193	191	189	187
- % chg	-1.0%	-1.0%	-1.0%	-1.0%	-1.0%
Abbott Share (%)	2.1%	3.2%	4.2%	5.3%	6.2%
Abbott TRX (MM)	4.1	6.2	8.1	10.0	11.7
Price/Rx (\$, avg)	\$35	\$34	\$32	\$33	\$34
Abbott Sales (\$MM)	\$139	\$199	\$265	\$335	\$399
R&D (\$MM)	\$30	\$30	\$30	\$30	\$20
SG&A (\$MM)	\$101	\$83	\$86	\$99	\$115
SMM (%)	88%	90%	90%	90%	91%
Div. Margin (\$MM)	(\$23)	\$44	\$95	\$138	\$174

10 year pre-tax NPV @ 12.5% = \$345MM

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$201MM

10 year post-tax ENVY @ 12.5% = TBD

**Key Assumptions:**

- U.S. approval August 2003
- Market is declining 1% per year on TRX basis
- 150 mg QD dosing for all indications
- 5 day AECEB & pharyngitis; 10 day CAP & sinusitis
- 5 day pack priced at parity to Zithromax; average price per RX shown is after discounts/rebates
- 800M details/year (62% primary, 38% secondary)
- Sampling at parity to current Biaxin levels on basis of courses of therapy sampled
- Peak market share = 6.9% (2009)
- U.S. R&D costs at 60% of total
- NPV does not account for potential cannibalization of Biaxin by ABT-773

**Forecast Update Plan:**

Forecast will be updated if necessary upon receipt of the phase IIIa data 2Q01.

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**C.4.2 Ex-U.S. Sales Forecast** The ex-U.S. sales forecast is shown in Table C.4.2a, below.

Table C.4.2a Ex-U.S. Forecast (Date of Forecast: 8/00)					
	2004	2005	2006	2007	2008
Market (MM packs)*	592	592	593	594	595
- % chg	0.0%	0.0%	0.1%	0.2%	0.2%
Abbott Share (%)	1.1%	2.3%	3.3%	4.3%	4.9%
Abbott packs (MM)	6.5	13.6	19.7	25.3	29.3
Price/Rx (\$)	12.6	12.6	12.6	12.6	12.6
Abbott Sales (\$MM)	82	172	248	321	373
R&D (\$MM)	4	2	2	2	2
SG&A (\$MM)	84	84	84	76	76
SMM (%)	85%	88%	89%	90%	90%
Div. Margin (\$MM)	(19)	63	132	199	254

10 year pre-tax NPV @ 12.5% = \$403MM      10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$234MM      10 year post-tax ENVY @ 12.5% = TBD

\* packs used as a proxy for Rx's (Rx's not audited in most AI markets)

**Key assumptions:**

- Ex-US launch lags U.S. by 6-18 months due to pricing negotiations and/or special registration requirements in AI markets
  - Europe (average): U.S. launch + 6 months = Q12004
  - LA (average): U.S. launch + 6 months (Q1 2004)
  - PAA (average): U.S. launch + 1 yr (Q3 2004)
  - Japan (average) = US launch + 1 yr (Q3 2004)
  - Canada = US launch + 12-18 mos (Q3 2004)
- Market is declining approximately 1-2.5% in Europe, Japan and Canada, but increasing approximately 2-3% in LA and PAA
- ABT-773 Pack Price = current Clari price per course of therapy
  - Europe: \$10.8./pack (150mg, 5 day); \$22.6/pack (300mg, 7day avg)
  - LA/Canada: \$13.4/pack (150mg, 5day); \$28.2/pack(300mg, 7 day avg)
  - PAA: \$9.7/pack; \$20.4/pack
  - Japan; \$12.8/pack; \$26.8/pack
- Peak Market share (2008): Europe = 6.0%; LA/Canada = 4.6%; PAA = 3.3%; Japan = 5.9%; 90% of pack share from 150mg QD dose strength
- Dosing = 150mg QD 5 day for bronchitis and pharyngitis; 300mg QD 10 day for CAP and sinusitis
- No resistance claim, however, language in label describing in vitro activity against resistant organisms

**Forecast Update Plan:**

Forecast will be updated by 12/00 after 2001 LRP forecasting cycle, incorporating input from AI affiliates.



### C.5 Facilitating Launch and Market Penetration

There are three components of the strategy to facilitate the launch of ABT-773. These are 1) promotional claims 2) communication strategy 3) opinion leader development. These activities are summarized in these sections below.

#### C.5.1 Desired Promotional Claims

Desired key message	Regulatory requirement	Measures	Timing	Study Number	Type of message	Feasibility	Severity Impact	Comments/Risk
Low potential for resistance development	TBD	Mutation frequency, sub-MIC serial passages, mutation prevention concentration	In progress	Multiple	In-vitro (implied efficacy)	Medium	Med	
Does not induce macrolide resistance	TBD	Ribosome kinetics, MIC evaluations	In progress	Multiple	In-vitro (implied efficacy)	Medium	Med	
Clebs against penicillin/mac resistant S. pneumoniae	~ 15 resistant isolates, high erad. rate	Patient isolates, erad rate (CAP)	5/2002	Phase III studies	Efficacy	Low	Med	
Lower resource utilization vs comparators	2 clinical studies	Overall disease cost	5/2002	Phase III studies	Economic	Low	Med	
Comparable cure/eradication rates to phase III comparators	Clinical studies	cure/erad rate	5/2002	Phase III studies	Efficacy	Medium	High	
Comparable safety/AE profile to phase III comparators	Clinical studies	safety/AE rate and severity; dropout rate	5/2002	Phase III studies	Efficacy	Medium	High	

#### C.5.2 Communication Strategy

Following is a summary of the activities to date relating to communication strategy:

- 83 posters have been presented at 8 scientific conferences between 1998-2000
- 8 journal articles have been published in two journals, all published in 2000
- Approximately 72 research studies have been completed, many with the intent to publish
- Approximately 87 research studies are in progress, many with the intent to publish
- Approximately 120 external investigators have completed or are in progress with research studies, many with the intent to publish

Much of the above work has dealt with microbiological and/or animal model data. As the compound moves forward, emphasis will shift to the release of more clinically relevant data. Scientific meetings and journals will continue to serve as the primary channels for dissemination of information, though more specialized communication (symposia, advisories, press releases, etc) will start to be used as a more complete understanding of ABT-773 is gained.

An additional focus of study/communication will be towards capitalizing on the unique ribosome binding properties of the product. Information gained from this initiative may be called upon in defense of the selection of the relatively low 150 mg dose. It may also serve as a means of differentiating the product. Various internal and external investigators are working to gain a greater understanding of the underlying science as well as the properties of ABT-773 in this area. Early in 2001 an internal/external "working group" will be convened to develop a strategy for further study in this area and for the optimal dissemination of this data.

Management of all aspects of the ABT-773 communication plan will be facilitated via an intranet tool currently in development by IM&T and external developers. The completion is targeted for November 2000.

### **C.5.3 Opinion Leader Development**

An ABT-773 advisory board of external opinion leaders has been established and has been convened several times over the last several years. The purpose of these advisories has been to solicit guidance for the development of ABT-773 as well as to positively influence their perception of the ketolide class and ABT-773 in particular. An additional mechanism for opinion leader development has been their involvement in both clinical and non-clinical studies. Approximately 120 external investigators, many regarded as top-tier opinion leaders, have experience with ABT-773. A major initiative as ABT-773 moves forward is to identify key national opinion leaders who have favorable experience/opinion of ABT-773 and to work with them to develop an advocacy strategy for publications, scientific meetings, symposia, and advisories.

## D. Regulatory Strategy

## D.1 Regulatory Strategy SWOT Analysis

Table D.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<ul style="list-style-type: none"> <li>QD dosing may be viewed as positive for patient compliance if data is strong</li> <li>If the drug has a favorable risk benefit ratio with added value compared to existing therapies then the likelihood of approvability is high in EU countries or other countries requiring a CPMP package</li> <li>ABT-773 may present a key point of differentiation with promising activity against macrolide and penicillin resistant <i>Streptococcus pneumoniae</i> and enhanced antibacterial activity <i>in vitro</i>. If proven <i>in vivo</i>, this may indicate favourable relative therapeutic value required for approval and inclusion within local use guidelines.</li> </ul> <p>For COFs countries, if the US or EU receives approval then approvals in these LA/PAA countries are assured assuming appropriate sourcing.</p>	<p>Make sure PK/PD data is available to support dose selection rationale</p> <p>The development programs must be designed to unequivocally demonstrate the existence of an added value (e.g. safety or clinical efficacy against resistance species)</p> <p>To utilize the enhanced bacterial activity as a key point of differentiation need to:</p> <ul style="list-style-type: none"> <li>• Ensure clinical program is designed to optimize chances of obtaining desired isolates</li> <li>• Ensure appropriate pk/pd studies are performed</li> <li>• Seek agreement from FDA regarding burden of proof for labeled indication against resistant pathogens</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>Take with food labeling is required to reduce AE's</li> <li>If BID is chosen for either CAP or ABS, diurnal variation may become an issue during FDA review</li> <li>Conformance to Abbott's &amp; FDA's Electronic Document Management System requirements may impact filing date</li> <li>High COG's for bulk drug driving vendor matrix and push to redefine starting material</li> </ul> <p>Harmonization of global clinical trial designs and</p>	<p>FDA will still require pivotal bioavailability studies to be done in fasted state.</p> <p>Justification must be provided</p> <p>Electronic filing likely to be valued very highly by FDA, so need to manage internal process to see that we can meet requirements</p> <p>Need FDA buy-in from End-of-Phase 2 CMC meeting on starting material and vendor matrix, including stability requirements</p> <p>Communicate with team, international affiliates, international experts and</p>

	<p>guidelines</p> <ul style="list-style-type: none"> <li>Differences in medical practice exist worldwide for antibiotics and associated infections</li> <li>Differences in comparator and dosing regimens</li> <li>Stringent EU regulatory environment with antibiotics</li> </ul> <p>EU filing will require a harmonized labeling therefore country-specific favourable labeling cannot be pursued (as done with clarithromycin)</p> <p>Two dose scenario with a lower dose chosen for ABECB, Sinusitis and Pharyngitis with a second dose chosen for CAP may provide limited numbers to assess safety of the higher dose</p> <p>Increased resistance awareness may influence stricter requirements and trend away from lowest effective dose</p>	<p>discuss with EU authorities through agency meetings to ensure design of trials and comparators are acceptable</p> <p>Discuss any country specific issues with authorities, international experts and affiliates. Monitor regulatory environment and competitive products.</p> <p>Discuss issue authorities at agency meeting and ensure MAA addresses this issue. May consider Phase IV studies to address this concern.</p> <p>Ensure clinical program includes relative pk/pd studies and can demonstrate clear efficacy at proposed doses. Ensure clinical program is designed to obtain resistance isolates</p>
Opportunities	<ul style="list-style-type: none"> <li>Labeling for resistant organisms if isolates are obtained</li> </ul> <p>Eligible for Centralised filing process which would provide EU-wide 10 year protection . May also file by Mutual Recognition procedure which more provides flexibility for non-harmonized disease practices (e.g. infectious disease/antibiotics)</p> <p>Once Daily Dosing may enhance compliance</p>	<p>Get agreement with FDA at End of Phase 2 meeting regarding number of isolates required for labeling claim</p> <p>Filing strategy to be determined based on strength of the clinical program and advice received from agencies during planned agency meetings</p>
Threats	<ul style="list-style-type: none"> <li>QT prolongation class labeling in Warnings section of labeling</li> <li>Liver enzyme increases in Warnings section of labeling</li> </ul>	<p>Get agreement with FDA at End of Phase 2 meeting regarding EKG monitoring in Phase 3 and promote theory that QT prolongation is not class related</p> <p>Ensure that non-clinical and clinical program fulfill the CPMP points to consider on QTc prolongation.</p> <p>Ensure that non-clinical and clinical program addresses potential safety</p>

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	<ul style="list-style-type: none"> <li>• Possible failure of short course therapy for Pharyngitis due to more stringent Test of Cure requirement from FDA</li> <li>• If gastrointestinal AE's are high, may affect benefit/risk assessment by FDA</li> <li>• Could be affected by CDC push to reduce antibiotic use; reserve use of drugs effective vs resistant organisms until existing therapies have failed</li> </ul>	labeling issues and MAA/NDA addresses these concerns.
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#### Registration Strategy and Timelines for Filing

Table D.2 Registration Strategy and Timelines for Submission		
REGION	Proposed Submission Date	Justification
US	August 2002	Estimated completion of the clinical program and CMC stability data
Europe Filing procedure (Centralised or MRP) to be determined based on strength of clinical data and discussion with authorities	August 2002	Estimated completion of the chemistry/pharmacy and clinical data
Japan Plan to bridge to US data assuming pk profile is similar in Japanese subjects and a successful Phase II bridging study is possible in Japan	TBD, after completion of Phase I local study in Japan.	Bridging obviates the need for a lengthy and expensive Japanese Phase III program. Requires Kiko agreement.

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**D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program**

<b>Table D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program</b>				
<b>COUNTRY</b>	<b>Guideline Requirement</b>	<b>Probability of Achieving</b>	<b>Impact on Filing</b>	<b>Impact on Approvability</b>
<b>US</b>	• Draft Anti-Infective Guidances for CAP, ABECB, ABS & Pharyngitis	High	High	High
	• Draft Anti-Infective Guidances – General Considerations for Clinical Trials	High	High	High
	• Anti-Infective Points to Consider document	High	High	High
	• ICH Efficacy Guidances – E1 through E12	High	High	High
	• ICH Safety Guidances – S1 through S7	High	High	High
	• ICH Quality Guidances – Q1 through Q7	High	High	High
<b>Europe</b>	All ICH guidelines as above, plus CPMP points to consider on QT prolongation CPMP guideline on the clinical evaluation of antibacterials DRAFT CPMP guideline for pk/pd	High/Moderate	High	High
<b>Japan</b>	All ICH guidelines as above plus local guidelines/JP issues. ICH E5 ethnic bridging guideline.	Moderate/Unknown	High	High

**D.4 Table of Proposed Discussions with Health Authorities**

<b>Table D.4 Table of Proposed Discussions with Health Authorities</b>		
<b>COUNTRY</b>	<b>Reason for Discussion</b>	<b>Proposed timing for Discussion</b>
<b>US</b>	• End of Phase 2 – Clinical	10/20/00
	• End of Phase 2 – CMC	TBD
	• Pre-NDA – Clinical	TBD
	• Pre-NDA – CMC	TBD
<b>Europe</b>	• Individual agency meetings with UK, Germany, France and Spain to discuss Phase III Clinical program trial designs	UK complete – 07/10/00 Germany complete- 07/21/00 France scheduled – 08/30/00 Spain – to be determined
	• Pre-filing meetings to be determined based on filing strategy	
<b>Japan</b>	• KIKO- discuss bridging strategy to 300 mg EU/US program	Complete – June 2000
	• KIKO – re-discuss dose justification	TBD

## E. Development Cost and Sensitivity Analysis

### E.1 Strategic Spending Overview

The tables below describe the major milestones for the ABT-773 Tablet program as well as the Phase II/III studies and associated costs.

Milestones	
Description	Date
DDC Meeting	3/1997
Start of first GLP animal tox study	6/1997
First dose in human (beg. Phase I)	12/1997
First dose in patient (beg. Phase II)	9/1999
First dose in Phase III	11/2000
Last Patient/Last Visit	4/2002
NDA Filing	8/2002
NDA Approval	8/2003
Europe (EMEA) Filing	8/2002
Europe (EMEA) Approval	8/2003
Japan Filing	TBD
Japan Approval	TBD

Protocol # - Study Name	Start (1 <sup>st</sup> Pt)	End (Last CRF)	R/OSS \$000	Total Target Patients	Actual Enrollment
M99-048, Phase II Dose Ranging, ABECB	9/1/99	3/31/00	3,885	300	384
M99-053, Phase II Dose Ranging, Sinusitis	9/1/99	4/30/00	3,172	300	292
M99-054, Phase II Dose Ranging CAP	9/1/99	4/30/00	4,089	300	187
M00-219 Phase III CAP, Dose Ranging	11/7/00	4/30/01	14,400	800	0
M00-216 Phase III ABECB vs Azithromycin US	11/7/00	4/30/01	7,381	600	0
M00-217 Phase III ABECB vs Levofloxacin EUR	11/7/00	4/30/01	4,600	500	0
M00-225 Phase III Sinusitis Dose Ranging	11/7/00	4/30/01	7,200	600	0
M00-223 Phase III Pharyngitis vs Penicillin US	11/7/00	4/30/01	4,340	520	0
M00-222 Phase III Pharyngitis vs Penicillin EUR	11/7/00	4/30/01	5,000	520	0
M00-226 Phase III Sinusitis vs Augmentin US	10/1/01	4/30/02	4,400	450	0
M00-220 Phase III CAP vs Amoxicillin EUR	10/1/01	4/30/02	5,700	500	0
M00-221 Phase III CAP vs Levofloxacin US	10/1/01	4/30/02	8,200	450	0
M00-218 Phase III Sinusitis vs quinolone TBD EUR	10/1/01	4/30/02	5,300	500	0



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**E.2 Base Case Scenario****E.2.a Base Case Scenario for Project:** \_\_\_\_\_

	Prior Years	1999	2000	2001	2002	
<b>Base Program</b>						
CMC	17.5	28.6	31.2	22.8	14.5	
- PARD/IDC	4.8	5.4	8.6	7.8	4.5	
- SPD	12.7	23.2	22.6	15.0	10.0	
Drug Safety	3.5	2.5	3.4	1.7	1.0	
Other:	7.4	7.7	5.0	4.6	4.0	
Total	28.4	38.8	39.6	29.1	19.5	
<b>Clinical Program</b>						
Registration	2.5	9.5	34.5	61.9	23.3	
Pricing						
Marketing						
Other:						
Total	30.9	48.3	74.1	91.0	42.8	287.1

**E.3 Upside Scenario****Funding Increase**

If funding were to be increased by 25%, how would that increased funding be used?

- 1) Accelerating Program
  - At this point in the program, additional funding will not accelerate the filing any earlier than the August 2002 date. The current program is intense and needs to be accomplished within a short timeframe. Probability of success in the current program is estimated at 50 to 60%.
- 2) Enhancing Program
  - The pediatric and IV formulations are currently not funded and could continue from the earlier work completed in 2000. Approximately \$21MM is required for the IV development and \$39MM for the pediatric development. The IV program would provide support for marketing this antibiotic for serious infections and help the marketing of the tablet, and the pediatric supports the marketing position that this is a safe drug.
- 3) Enhancing Program within Existing Program
  - Additional funding within the current program would allow for additional patient enrollment incentives or an increase in the number of sites participating in the current Phase III program. This would increase the probability of success in achieving the Aug 2002 filing date.

**E.4 Downside Scenario****Funding Decrease**

If funding were to be decreased by, how would that decrease be applied?

- 1) Slowing Program
  - A decrease in program spending would delay the filing of ABT-773 significantly, minimum one year, as RTI indications are seasonal, and the majority of patient enrollment comes from the northern hemisphere.
- 2) Trimming Program
  - Eliminating an indication will cause this filing to be unapprovable as the number of required patients on drug and the four indications being sought are the minimum RTI indications for approval. The program is only funded currently for one formulation.
  - The current program is currently funded at the minimal acceptable level for approvability by both FDA and AI regulatory agencies.
- 3) Increasing Risk
  - Refer to Item 2 above. Current probability of success for the program is 50 to 60%. Any reduction to the program will significantly delay the filing.



## F. Pharmacokinetics/Pharmacodynamics/Phase 1

### F.1 PK/PD/Phase 1 SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-773 are discussed below:

Table F.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	Phase IIb clinicals and PK/PD data support once daily dosing.  Food has no influence on ABT-773 PK. High drug levels in alveolar macrophages.	Conduct Phase III for ABECB and pharyngitis at 150mgQD. Further examine 150mgQD for AMS & CAP. Tolerability may require administration with food. This may explain efficacy vs. <i>H. flu.</i>
Weaknesses	ABT-773 may require a total daily dose of 300mg for severe infections.  ABT-773 is metabolized by and inhibits CYP3A; has potential to cause clinically important drug interactions.  ABT-773 has low & variable oral bioavailability. Absorption "window" makes ER dosage forms not feasible.	Examine 150mg BID for AMS & CAP and conduct tissue level studies.  Lowest effective dose (150mgQD) may minimize drug interaction potential.  Multiple ER dosage forms tried, none provided adequate bioavailability and true extended release <i>in vivo</i> .
Opportunities	At 300mgQD, ABT-773 inhibits CYP3A, but inhibition is less than 250mgBID clarithromycin.	May wish to repeat midazolam (CYP3A substrate) interaction study at 150mgQD or BID.
Threats	Disappointing ABT-773 tissue levels (especially WBC and ELF). Competition (Ketek™) reports higher WBC and ELF levels.	Repeat tissue level studies and in the meantime focus on efficacy data.

### F.2 PK/PD (Clinical)

The Phase 1 program consists of pharmacokinetic, special population, interaction and tissue penetration studies as outlined in section F.3. To attempt to design a once daily dosage form with optimal pharmacokinetics, fifteen prototype formulations were developed for the initial investigations of preliminary safety and pharmacokinetics. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen for further development based on

pharmacokinetics, safety, and ease of manufacture. Studies in special populations, drug-drug interaction assessments and tissue penetration evaluations have been conducted with formulation IR-C.

Table F.2.a lists all the completed, planned and proposed PK/PD clinical trials for ABT-773:

Table F.2.a: Clinical PK/PD Trials (Phase 1)					
STUDY	POPULATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M99-105	Healthy Adults	PK of ABT-773 in WBC Relative to Plasma	N = 8	Study completed	Poor partitioning of ABT-773 into WBC.
M99-007	Healthy Adults	Compare Concentrations of ABT-773 in BAL & AM to Plasma	N = 43	Study completed	High concentrations of ABT-773 in AM. Relatively low concentrations in ELF.
M99-142	Healthy Adults	Compare Concentrations of ABT-773 in BAL, ELF, AM, CSF & TLT to Plasma	BAL = 50 CSF = 10 TLT = 10	Ongoing	

### F.3 Phase 1 Overall Summary

#### Pharmacokinetic and Safety Studies:

In the first Phase 1 study (M97-716), the pharmacokinetics and safety of ABT-773 (IR-A) were assessed following rising single oral doses (100 – 1200 mg). This study was conducted in two parts with Part I consisting of single rising doses under fasting conditions and Part II a food effect assessment at a single dose of 400 mg. The pharmacokinetics of ABT-773 were linear over the 400 mg to 1200 mg dose range. At doses below 400 mg, the pharmacokinetics appeared to be nonlinear, with AUC increasing more than proportionally with dose. More recent data have indicated that safe and effective doses of ABT-773 in patients will likely be below 400 mg/day and that pharmacokinetic nonlinearity will occur at these clinically-relevant doses. The mean half-lives over the 200 – 1200 mg dose range were between 5.3 - 6.7 hours.

Administration of ABT-773 under nonfasting conditions had little or no effect on the pharmacokinetics. The most commonly reported adverse events were taste perversion and/or events related to the gastrointestinal system including abdominal pain, nausea, vomiting and diarrhea. Administration of ABT-773 with food decreased or eliminated the gastrointestinal adverse events but did not affect the incidence of taste perversion.

In the second Phase 1 study (M97-796) the pharmacokinetics and safety of ABT-773 (IR-A) were assessed in a multiple rising dose study. Total daily doses ranging from 200 mg to 1000 mg were administered for seven days. Over the multiple dose range of 200 to 500 mg BID and 200 to 300 mg TID, the pharmacokinetics of ABT-773 appeared to deviate from dose proportionality and time-linearity. The AUCs increased more than proportionally with increasing dose, and accumulation from single- to multiple-dose administration was greater than predicted. At steady state, the half-life ranged between 6.0 and 8.8 hours. ABT-773 pharmacokinetics exhibited diurnal variation, with lower C<sub>max</sub> and AUC values for doses administered in the afternoon or evening than for doses administered in the morning. In groups who were administered total daily doses of  $\geq 600$  mg of ABT-773, the most frequently reported adverse event was taste perversion.

In the third Phase 1 trial (M98-889) the relative tolerability of two doses of ABT-773, 100 mg TID and 200 mg TID, was compared with that of clarithromycin 500 mg BID in 153 healthy volunteers. There were no significant differences between the incidence of adverse events between the three regimens except for taste perversion which occurred in 8% of subjects receiving ABT-773 100 mg TID, 34.6% of subjects receiving ABT-773 200 mg TID and in 37.2% of subjects receiving clarithromycin.

Three Phase 1 trials were performed to compare steady state pharmacokinetics and safety after five days of treatment with various doses of ABT-773 (IR-A); 100 mg TID vs. 200 mg TID (M99-011), 300 mg once daily vs. 200 mg once daily vs. 100 mg TID (M99-016) and 100 mg BID vs. 200 mg BID (M99-018). Over these dose ranges, the pharmacokinetics of ABT-773 deviated from linearity. As seen previously, the AUCs increased more than proportionally with dose.

#### **Bioavailability Studies:**

Two Phase 1 studies (M98-865 and M98-885) were performed to evaluate the pharmacokinetics of 600 mg once daily doses for four extended-release prototypes of ABT-773 (two per study) administered with food for four days in comparison to formulation IR-A. For the four prototypes, plasma concentration profiles were much lower than those produced by the immediate release reference capsule. As a result, none of these prototypes continued in development.

Seven further Phase 1 trials (studies M99-023, M99-024, M99-025, M99-026, M99-029, M99-035, M99-042) were conducted to evaluate the pharmacokinetics and safety of ten additional ABT-773 prototypes, two immediate release and eight extended release formulations in comparison to the reference formulation (IR-A). All studies had two, three or four period cross-over designs with nonfasting, multiple once daily or BID ABT-773 5-day dosing in healthy volunteers. Pharmacokinetically, none of the extended release prototype formulations had superior bioavailability compared to the immediate release capsule. In addition, an Intelisite® study (M98-992, not included in the data package) investigating the absorption of ABT-773 confirmed that absorption of ABT-773 from the colon is limited. Due to the solubility profile of the drug, the apparent narrow absorption window, and low absorption from the colon, it appears that an extended release formulation is not feasible. Therefore, optimal bioavailability is expected with an immediate-release formulation rather than extended release formulations. Upon review of the preliminary data, the immediate release formulation (IR-C; M99-024) was chosen for further development as it appeared to be the most robust formulation and demonstrated fewer adverse events and drop-outs than IR-B (M99-023).

Additional biopharmaceutics studies will be conducted to characterize the relative bioavailability/bioequivalence and food effect on the final, production-scale tablet formulation proposed for marketing.

Table F.3.a lists all the completed, planned and proposed clinical trials for ABT-773:

Table F.3.a: Clinical Trials (Phase 1)					
STUDY	POPULATION	OBJECTIVE/PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M97-716	Healthy Adults	Rising Single Oral Doses of ABT-773 in Nonfasting and Fasting Subjects	Part 1 = 56 Part 2 = 24	Study complete	ABT-773 PK were nonlinear. Food has no effect on ABT-773 PK
M97-796	Healthy Adults	Rising Multiple Oral Doses of ABT-773	N = 83	Study complete	ABT-773 PK were nonlinear and had diurnal variation. If the final to-be-marketed regimen is QD, FDA may ask an AM vs. PM PK study.
M99-992	Healthy Adults	ABT-773 PK Comparing Oral IR Capsule to Intellisite® Capsule (Targeted Release in Colon)	N = 10	Study completed	ABT-773 is very poorly absorbed from colon.
M99-011	Healthy Males	ABT-773 PK Comparing 100mgBID to 200mgBID	N = 12	Study completed	ABT-773 AUC increased more than proportionally with dose and had diurnal variation.
M99-016	Healthy Males	ABT-773 PK Comparing 300mgQD & 200mgQD to 100mgTID	N = 24	Study completed	ABT-773 AUC increased more than proportionally with dose and greater exposure achieved by QD vs. TID dosing.
M99-018	Healthy Males	ABT-773 PK Comparing 100mgBID to 200mgBID	N = 24	Study completed	ABT-773 AUC increased more than proportionally with dose and had diurnal variation.
M99-024	Healthy Males	ABT-773 PK Comparing 150mg IR-C Tablet to 100mg Capsule	N = 18	Study completed	Prototype C tablet was bioequivalent to the reference capsule. Greater exposure achieved by QD vs. BID dosing.



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Table F.3.a: Clinical Trials (Phase I) Cont.					
STUDY	POPULATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
Special Population Studies					
TBD	TBD	Effects of Age and Gender on ABT-773 PK		Protocol TBD	ABT-773 clearance may increase with age. Clarithromycin AUC higher in females than in males.
M99-127	Severe Renal Impaired vs. Healthy	Effects of Renal Impairment on ABT-773 PK		Protocol in progress	No effect of renal impairment on ABT-773 PK expected.
M99-119	Healthy Adults	ABT-773 Single and Multiple Dose Ranging PK in Japanese vs. Non-Japanese	N = 84	Study completed	At equal doses, Japanese had about 50% greater plasma ABT-773 concentrations than non-Japanese. Lower dose needed in Japanese patients.
M99-126	Mild & Moderate Hepatic Impaired vs. Healthy	Effects of Hepatic Impairment on ABT-773 PK	N = 24	Ongoing	

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Table F.3.a: Clinical Trials (Phase 1) Cont.					
STUDY	POPULATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
Drug Interaction Studies					
M99-128	Healthy Adult Females	Effects of ABT-773 on the PK of OCs	N = 18	Study completed	No clinically significant drug interaction was observed.
M99-138	Healthy Adults	Effects of Ketoconazole (CYP3A inhibitor) on PK of ABT-773	N = 18	Study completed	Ketoconazole inhibited ABT-773 metabolism increasing ABT-773 AUC >5 times.
M99-139	Healthy Adults	Effects of ABT-773 on the PK of Theophylline	N = 18	Study completed	No clinically significant drug interaction was observed.
M00-155	Healthy Adults	Effects of ABT-773 on the PK of Midazolam (CYP3A substrate)	N = 24	Study completed	ABT-773 inhibited midazolam metabolism doubling midazolam AUC. Interaction smaller than interaction between clarithromycin and midazolam.
M00-156	Healthy Adults	Effects of Rifampin (CYP3A inducer) on PK of ABT-773	N = 18	Study completed	Rifampin induced ABT-773 metabolism decreasing ABT-773 AUC by >90%. ABT-773 should not be given with any drug that might induce CYP3A.
TBD	Healthy Adults	Assessment of the Pharmacokinetic Interaction Between ABT-773 and Warfarin	TBD	Protocol TBD	R-warfarin is a CYP3A substrate and warfarin is a NTI drug.
TBD	Healthy Adults	Assessment of the Pharmacokinetic Interaction Between ABT-773 and Digoxin	TBD	Protocol TBD	Digoxin is a Pgp substrate and a NTI drug.

#### Drug Interaction Program

As indicated in the Phase 1 clinical overview, further studies in special populations and drug-drug interaction assessments will be conducted. Preliminary pharmacokinetic data are available from five drug interaction studies. Because ABT-773 will be administered to women who rely upon oral contraceptives for birth control, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of the components of a commonly-used combination oral contraceptive product (Ortho-Novum 1/35). Because ABT-773 will be co-administered with

theophylline in bronchitis patients, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of theophylline. Because ABT-773 is known to be a substrate and inhibitor of the cytochrome P450 3A4 isoform subfamily (CYP3A4) in vitro, three clinical drug-drug interaction studies suggested in FDA Guidance on in vivo drug metabolism/drug interaction were conducted. Because ABT-773 is a CYP3A4 substrate, we have examined the effects of the CYP3A4 inhibitor, ketoconazole, and the inducer, rifampin, on the pharmacokinetics of ABT-773. Because ABT-773 may be an inhibitor of CYP3A4 in vivo, we have examined the effects of ABT-773 on midazolam pharmacokinetics. Preliminary pharmacokinetic and safety data are also available from a special population study in Japanese subjects.

In addition to these five completed drug-drug interaction studies, the effects of ABT-773 on the pharmacokinetics of warfarin and digoxin will be examined. A special population study to examine the effects of mild and moderate hepatic impairment (Child-Pugh) on ABT-773 is ongoing. Because no more than 10% of ABT-773 is excreted in the urine, a reduced-design study to examine the effects of severe renal impairment (creatinine clearance: 10-29 mL/min) on ABT-773 will be conducted. An additional special population study will be conducted to examine the effects of age and gender on ABT-773 pharmacokinetics.

## G. Clinical Trial Program

### G.1 Clinical Trial Program SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-XXX are discussed below:

Table G.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<ol style="list-style-type: none"> <li>150 mg QD dose should minimize side effects and provide sufficient exposure for efficacy.</li> <li>Complete Pharyngitis and ABECB comparative Phase III studies by 2Q, 2001, and concentrate thereafter on CAP and ABS.</li> </ol>	<ol style="list-style-type: none"> <li>Two studies using this dose, two studies comparing it to higher dose for further evaluation in CAP and sinusitis.</li> <li>Prepare all documentation for NDA/regulatory filings before CAP and sinusitis studies complete.</li> </ol>
Weaknesses	<ol style="list-style-type: none"> <li>AE profile – GI, taste, at 300mg significantly higher than clari 500mg BID.</li> <li>Completion of CAP and sinusitis studies comparing 150 QD and BID may not occur by 2Q, 2001, delaying start of other pivotal studies.</li> <li>Further changes/amendments to protocols.</li> <li>Fail to enroll CAP and sinusitis patients early in season for Phase III trials starting 3Q, 2001.</li> </ol>	<ol style="list-style-type: none"> <li>Use lower dose (150 mg QD).</li> <li>Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Monitor data carefully and stop study if significant trend towards one arm.</li> <li>Amendments will not be finalized until studies are initiated with original protocols.</li> <li>Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Add South American sites if needed (2002).</li> </ol>
Opportunities	<ul style="list-style-type: none"> <li>Claim for resistant organisms.</li> </ul>	<ul style="list-style-type: none"> <li>Conduct studies in geographical locations where resistant bacteria are prevalent. Use central labs wherever possible.</li> </ul>
Threats	<ul style="list-style-type: none"> <li>Studies being done by other sponsors.</li> </ul>	<ul style="list-style-type: none"> <li>Pay appropriately; maximize contact with investigators. Hold successful investigator meetings and use retainer fees if necessary.</li> </ul>

## G.2 Clinical Trials

Table G.2.a lists all the planned and proposed clinical trials for ABT-773:

Table G.2.a: Clinical Trials (Phase 2-3)					
STUDY	PHASE	OBJECTIVE/ PURPOSE OF STUDY	# OF PTS	FUNDED ?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M00-219	III	CAP; 773 150 QD vs. 150 BID	800	Yes	11/2000 - 4/2001, 50% likely to finish on time.
M00-216	III	ABECB; comparing AZI vs. 773	600	Yes	11/2000 - 4/2001, 100% likely to finish on time.
M00-217	III	ABECB; comparing Levo vs. 773	500	Yes	11/2000 - 4/2001, 100% likely to finish on time.
M00-225	III	Sinusitis; 773 150 QD vs. 150 BID	600	Yes	11/2000 - 4/2001, 50% likely to finish on time.
M00-223	III	Pharyngitis; comparing penicillin (250 mg TID) vs. ABT773	520	Yes	11/2000 - 4/2001, 100% likely to finish on time. There is some chance that it will not meet FDA standards of >85% at 30 days.
M00-222	III	Pharyngitis; comparing penicillin (500 mg TID) vs. ABT773	520	Yes	11/2000 - 4/2001, 100% likely to finish on time.
M00-221	III	CAP; comparing Levo vs. 773	450	Yes	09/2001 - 04/2002, 50% likely to finish on time.
M00-220	III	CAP; comparing Amoxicillin vs. 773	500	Yes	09/2001 - 04/2002, 50% likely to finish on time.
M00-226	III	Sinusitis; comparing quinolone TBD vs. 773	450	Yes	09/2001 - 04/2002, 75% likely to finish on time
M00-218	III	Sinusitis; comparing Augmentin vs. 773	500	Yes	09/2001 - 04/2002, 75% likely to finish on time

### Phase 2

In Phase 2a study M98-967, subjects with ABECB were treated with 100 mg TID or 200 mg TID dosing regimens which resulted in high clinical and bacteriological cure rates (see Section 9.3).

Three Phase 2b studies (see Section 9.4) conducted in both the US and EU investigating ABT-773 once daily doses have been completed:

- M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days)
- M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days)
- M99-048 - Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)

### Phase 3

The Phase 3 program consists of trials originating in either the United States or Europe comparing the safety and efficacy of ABT-773 in the proposed indications as described below.

- Community Acquired Pneumonia (total n ~ 1200 for ABT-773 arms)
  - M00-221 - One pivotal United States Phase 3, Controlled Study
  - M00-219 - One pivotal United States Phase 3, 2 Dose Study
  - M00-220 - One supportive European Phase 3, Controlled Study
- Acute Bacterial Exacerbation of Chronic Bronchitis (total n ~ 500 for ABT-773 arms)
  - M00-216 - One pivotal United States Phase 3, Controlled Study
  - M00-217 - One supportive European Phase 3, Controlled Study
- Acute bacterial sinusitis (total n ~ 1000 for ABT-773 arms)
  - M00-226 - One pivotal United States Phase 3, Controlled Study
  - M00-225 - One pivotal United States Phase 3, 2 Dose Study
  - M00-218 - One supportive European Phase 3, Controlled Study
- Pharyngitis (total n ~ 500 for ABT-773 arms)
  - M00-223 - One pivotal United States Phase 3, Controlled Study
  - M00-222 - One supportive European Phase 3, Controlled Study

### Strategy of Clinical Program

A global clinical development program has been implemented intended for world-wide registration. An estimated total of 5,500 subjects will be enrolled in the Phase 3 clinical program including both study drug and comparator. Approximately 3,500 subjects world-wide will be available for the efficacy evaluation of ABT-773. An estimated total of 5,300 subjects will be available for the safety evaluation of ABT-773 including Phase 1/2/3 data.

#### 1. ABT-773 Dose Selection for Phase 2a Study in ABECB (M98-967)

ABT-773 is a potent antibacterial agent with *in-vitro* activity against community-acquired respiratory pathogens including *S. pneumoniae*, (including penicillin-resistant and macrolide-resistant strains; PRSP and MRSP) *H. influenzae*, *S. pyogenes*, *M. catarrhalis* and atypical organisms including *Mycoplasma spp.*, *Chlamydia spp.* and *Legionella spp.* It also has activity against anaerobic gram-positive bacteria found in the normal upper respiratory tract and the bowel flora.

In addition, ABT 773 has been shown to demonstrate *in vivo* efficacy in animal model pulmonary infection studies against these prevalent respiratory pathogens.

The highest MIC exhibited to ABT-773 among respiratory pathogens (including PRSP/MRSP) is that of *H. influenzae*. The MIC<sub>90</sub> ranges from 2-4 µg/ml. In rat lung efficacy studies the CFU reduction in rat lung ( $2 \log_{10}$  -  $3 \log_{10}$ ) was exhibited by an AUC of 2.4-9.4 µg•hr/ml when the drug was administered as a BID regimen.

Unformulated drug was delivered in capsules as QD, BID and TID regimens in dose-escalating single and multiple dose studies (100 mg QD as lowest dose) in order to evaluate the PK properties and safety profile, and to determine the dose regimen for the Phase 2a study.

The three key factors considered in selecting the dose and frequency of dosing for the Phase 2a study from the Phase 1 dose-escalating studies were; the AUC range necessary to treat *H. influenzae* in animal model studies, the safety profile of the drug, and the goal to simulate an extended release profile for eventual once daily dosing.

Based on these considerations 100 mg TID and 200 mg TID dose regimens were selected for Phase 2a study M98-967. The mean AUCs for these regimens determined in Phase 1 studies were approximately 4.1 µg•hr/ml and 14.9 µg•hr/ml, respectively.

## 2. Dose Selection for Phase 2b Studies ABECB (M98-048), ABS (M98-053) and CAP (M98-054)

In several Phase 1 studies the mean AUC for 300 mg QD (3 x 100 mg capsules) ranged from 4.8-8.0 µg•hr/ml. The mean AUC values for the QD regimen were higher in all four Phase 1 studies than for TID regimen, and additionally, in one Phase 1 cross-over study (5.9 vs. 4.1 µg•hr/ml) due to some extent of diurnal variation in absorption.

The efficacy/safety results of 100 mg TID (M98-967) were excellent. The clinical and bacteriological cure rates were both 98% and adverse events were low with the exception of 11% diarrhea. The study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Pharmacokinetic data from a subset of subjects in this study indicated that the mean AUC for this regimen was 5.5 µg•hr/ml. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patient compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen (plasma mean AUC values of 4.1 and 5.9 µg•hr/ml, respectively) as discussed

above. In addition, the 300 mg dose administered QD had a mean  $C_{max}$  value of 0.9  $\mu\text{g/ml}$ , which together with the exposure outlined above, provides adequate coverage for bactericidal activity against PRSP/MRSP with  $\text{MIC}_{90}$  of 0.12.

Phase 2b studies were initiated with an immediate release tablet after multiple prototype extended release tablets failed to yield AUC values similar to that of the immediate release capsule and did not exhibit the desired extended release profile. Therefore, 150 mg immediate release tablets were manufactured and demonstrated to be bioequivalent to capsules (150 mg x 2 tablets vs 100 mg x 3 capsules) and were used in all three Phase 2b studies.

The 300 mg QD middle dose was bracketed in two of the dose-ranging Phase 2b studies (ABECB and ABS) with 150 mg and 600 mg doses to explore the optimal efficacy and safety range of the drug. In CAP, only 300 mg and 600 mg QD doses were used.

### 3. Dose Selection for Phase 3 Studies

The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABECB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.

The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.

Overall eradication of *S. pneumoniae* was excellent in all three studies. The data suggested that there was no apparent relationship between MIC and eradication or persistence of the isolates in the three trials, as would be expected with a susceptible population. There were no significant differences in eradication of *S. pneumoniae* between the dose groups in each of the trials and no evidence of development of resistance or of an increase in MIC in persistent isolates. Four MRSP isolates (2 *mefI*/2 *erm*) were eradicated at the 150 mg dose in the ABECB study.

Regarding *H. influenzae*, overall eradication rates were high in ABECB and CAP. There were too few isolates in ABS to draw any conclusions. The data suggested that eradication or persistence was not predicted by the MIC value again consistent with a susceptible population where occasional persistent isolates are seen. Differences in eradication of *H. influenzae* were not significant between the dose groups in the three studies. For *H. influenzae*, 17/18 (94%) isolates were presumed eradicated in the ABECB study in the 150 mg arm of the study. The number of



*H. influenzae* isolates in the ABS study were too few to reach a meaningful conclusion (3/5) of presumed eradication.

There were no statistically significant differences between the 150 mg and 300 mg arms of the clinical outcome in ABECB and ABS studies, and the confidence intervals suggested they were equivalent in clinical outcome. However, 150 mg was tolerated better as far as taste disturbance and GI adverse events.

ABECB/Pharyngitis - Since both confidence intervals and statistical tests suggested that 150 mg and 300 mg dose groups were similar in both clinical and bacteriological outcome, it was decided to proceed into Phase 3 for ABECB indication with two studies using a 150 mg QD dose for 5 days. It was also decided to use this dose in the pharyngitis/tonsillitis studies, based on excellent *in vitro* activity of this drug against *S. pyogenes*, including macrolide resistant strains.

ABS - Excellent clinical activity was demonstrated in the 150 mg arm. Due to low pathogen recovery rate in this study, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID (with sinus punctures) in lieu of the open single dose Phase 3 study as recommended in the FDA guidance document. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed. For this first study, 150 mg BID was selected since this regimen has been shown to have a lower  $C_{max}$  compared to 300 mg QD, thus potentially resulting in less taste disturbance and possibly lower GI side effects. In addition, the AUC values (3.9-5.8) obtained in Phase 1 studies are within AUC values of 150 mg and 300 mg QD, two doses that were shown to be effective in this indication.

CAP - For this indication, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID in lieu of the open single dose Phase 3 study as recommended in the guidance document. The 150 mg QD dose was included, although it was not evaluated in the Phase 2b study, it exhibited efficacy in the ABECB and ABS Phase 2b studies. The 150 mg BID was selected due to its potentially lower taste disturbance and GI adverse event profile compared to 300 mg QD. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed.

#### 4. Selection of comparators for Phase III studies

Selection of comparators were based on input from PPD, AI and affiliate marketing groups, medical and regulatory members of PPD and AI and finally input from three regulatory agencies

in Europe (UK, France and Germany) as well as US FDA Anti-Infective Division. A total of 10 studies are planned to be conducted. Two studies in ABECB, one in Europe and one in US. The European study will be vs Levofloxacin and US study vs Azithromycin. Both drugs have major market shares in this indication, Azithromycin in US and Levofloxacin is gaining momentum in Europe.

There are three planned studies for ABS, including two comparative studies vs Augmentin. And the two dose ABT 773 study. Augmentin is a key product in this indication both in US and Europe. In all probability, for the European study, Augmentin will be replaced with a quinolone. The plan will be finalized shortly.

The plan for acute streptococcal pharyngitis (ASP) calls for two studies against the standard treatment ; Penicillin V. 500mg tid, one in US and the second in Europe.

The CAP plan calls for three studies, the first, a two dose study of ABT 773 followed by a comparative study in Europe vs Augmentin and a comparative study in US vs Levofloxacin. Both products are used in this indication and it will be important to compare the efficacy/safety profile of ABT 773 with these agents. In all probability, for the European study, Augmentin will be replaced with a Amoxicillin 1gm TID. The plan will be finalized shortly

## H. Chemistry, Manufacturing and Controls

### H.1 Chemistry, Manufacturing and Controls SWOT Analysis

Table H.1 SWOT analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	Over 3600 kg of bulk drug have been successfully manufactured with overall yields improving from 21% to greater than 30%. Excellent progress on improving costs of bulk drug, currently less than \$6500/kg with target of \$2500/kg at launch.	Produce required development quantities of bulk drug to meet the cost targets at launch. Continue to obtain yield improvements through process work and manufacturing volume.  Obtain Regulatory approval (both AI and FDA) to identify intermediate step 5 as a starting material to allow for further process improvements at the earlier steps of manufacturing.
	Registration runs incorporated qualifying vendors for intermediates that will drive further bulk drug cost reductions and assure availability of bulk drug.	Continue to decrease cost of intermediates through use of three to four vendors.
	Formulation is a familiar technology, immediate release QD formulation manufactured by wet granulation.	Utilize an integrated scale-up program with both PARD and IDC to assure that a single formula/process will be used worldwide.
	Two sites of final product manufacturing (one in the U.S. and one in AI) at launch.	Two manufacturing sites provides back up support to AI and future potential back up to the U.S.
Weaknesses	Current bulk drug process requires 9 steps and high cost side chain which may limit potential cost improvements beyond launch.  ABT-773 has a bitter after taste as a result of excretion into the saliva that cannot be masked in the formulation. This is the most frequent adverse event identified in the Phase II clinicals.	Process development underway to evaluate optimized/new chemistry routes and potential to simplify the manufacturing process.  The 150 mg tablet minimizes after taste problems however, this will be a challenge in formulating a pediatric product.
	Phase III clinicals and NDA stability will be performed using an intermediate scale formulation.	A bioequivalency study will be performed linking the 10L bench formulation used in the Phase II clinicals, to the 300L intermediate formulation used in the Phase III clinicals, to the commercial scale (1200L U.S. and 600L U.K.) formulations.
	Due to Regulatory issues, there will not be a back-up site for the U.S. at launch.	Evaluate a separate project to obtain second site approval for the AI site to provide back up to the U.S.
Opportunities	Experience with bulk drug substance in terms of physical properties will allow us to develop specifications to improve consistency in formulation.	Particle size analysis is ongoing to provide data to support defining physical specifications by January 2001.

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	Obtaining regulatory approval for definition of step 5 as starting material will provide more opportunity for process improvements to reduce COGs	SPD, PPD and AI are collaborating on a solid data package to defend our step 5 starting material definition. An end of Phase II CMC meeting will be scheduled at the end of 2000 with FDA to discuss our strategy. Early discussions with the U.K. regulatory agency were optimistic.
Threats	Having one site for bulk drug can always carry risks.	A second site (Puerto Rico or Italy) will be considered in 2001 based on marketing forecast and capacity.

## H.2 SPD/PPD Chemical Sciences

SPD has made significant breakthroughs since 1997 to bring the cost of drug from \$30M to \$6.5M. Further reductions are expected by reducing the cost of the PQC side chain (competitive bidding among vendors), reducing the number of process steps, reducing the number of intermediate isolations, and increasing the batch size. An ongoing analysis of the assembly process is being made to evaluate the efficiencies gained in various steps in the process, and/or outsourcing a series of steps. The cost of drug during the filing year, 2002 is anticipated to be about \$2500/Kg.

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**Bulk Drug Requirement**Project: ABT-773 Adult Tablet

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Inventory Balance

964kg

End Q4 1999

Bulk Deliveries			Usage (Quantity)				
	Description	Quantity	Clinical	Formulation	Scale-Up	Inventory	
Q1 2000	Campaign 6, pre-NDA run	321.2 kg	321.2kg				1285.2kg
Q2 2000	Campaign 7, 8, 9 NDA runs	1008.9 kg			1008.9kg		2294.1
Q3 2000	Campaign 10, NDA run, Cam 11,12 dev runs	1029.9 kg			1029.9 kg		3324kg
Q4 2000	Campaigns 13, 14 development runs	670 kg			670 kg		3994kg
Q1 2001	Campaign 15, 16 development runs	670 kg			670 kg		4664kg
Q2 2001	Shut down for facility upgrade						4664kg
Q3 2001	Campaign 17	335 kg			335 kg		4999kg
Q4 2001	Campaign 18,19	670 kg			670 kg		5669kg

Lead Time (request to delivery; weeks) 6 mo

Comments:

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ABBT205007

**Schedule B ABT-773 Bulk Drug Usage - Tablet Formulation**

Task	Start	Finish	Task Use
1 10L Formulation Prototypes	Nov/09/98	Jun/30/99	107.8
12 75L Process Dev't/Bulk Drug Eval (24 runs, 200 kg)	Aug/23/99	Oct/01/99	151.0
Clinical Re-Supply PH II	Sep/08/99	Sep/08/99	5.4
14 Dissoln Method Justification Biostudy- Clin Mfg - 3 runs	Oct/04/99	Nov/15/99	24.0
16 Process Dev/Bulk Drug Eval 75L Pt2 (8 runs, 66.4 kg)	Nov/16/99	Dec/10/99	59.0
18 UK Site/2nd Process Verification 25L (33 kg)			
Batches 1-3	Dec/01/99	Jan/31/00	10.0
Batches 4-6	Feb/01/00	Mar/13/00	10.0
Batches 7-10 (two batches)	Mar/14/00	Oct/11/00	13.2
22 Proc. Supportive Dev, 75L Pt3 (16 runs-rep. Scale; 132.8kg)	Dec/13/99	Feb/04/00	132.8
24 75 L Bulk Drug Eval Pt 3 (10 runs; INCL cmpn 6 re-work)	Feb/01/00	Dec/01/00	84.7
26 Process Dev 300L (4 runs; 133.2 kg)	Jan/10/00	Feb/04/00	130.0
Phase III Clin Supply mfg, 75L Gral, 300 mg white, 62-329-AR	Mar/14/00	Mar/21/00	16.1
75L, 200 mg IR-D, lot 65-362-AR	May/22/2000	Jul/14/2000	24.1
28 Process Dev Pre-NDA (11 runs; 365.3 kg)	Feb/07/00	Apr/14/00	364.0
300L Gral, 300 mg IR-D ScaleUp Lot; 65-015-4Q	May/31/2000	Jun/13/2000	64.2
150 mg switch		0	
150 mg factorial compression study			24.0
150 mg tablet coating study			56.0
33 Mfg. NDA Runs - 1 Strength (4 lots/10 runs; 333kg)			
34 NDA Lot 1 (Abbott; Cmpgn 7-rework)	?	Jul/17/00	66.6
NDA Bio Lot 2 (ChemiSpa), Phase III supplies; 66-018-4Q	Jul/31/00	Aug/11/00	66.6
NDA Lot 3 (Uquilfa); 67-021-4Q	Sep/25/00	Oct/06/00	66.6
NDA Lot 4 (Taisho)	Sep/25/00	Oct/06/00	66.6
39 Process Verification 65 L (146 kg)	Feb/07/00	Sep/29/00	
Batches 1-6	Oct/18/00	May/31/00	50.0
Batches 7-12	Jun/01/00	Jul/31/00	50.0
Batches 12-15 (two batches)	Aug/01/00	Mar/26/01	35.0
Biobatch, 65L vs 300L (20 kg)	May/01/01	May/31/01	20.0
46 Process Dev 1200 L (4 runs, 532 kg) +1 run?= 665kg	Jan/22/01	Mar/05/01	665.0

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50 1200L Def Bio & Registration Lots (3 lots, 4 runs; 532 kg)	Mar/06/01	Jul/09/01	532.0
Definitive Biostudy, 300L vs 1200L	May/29/01	Jun/25/01	
57 75L Supportive Dev (For the 1200L, 20 runs; 166 kg)	Jan/17/01	Aug/23/01	166.2
58 300L Supportive Dev (For the 1200L, 5 runs; 166.5 kg)	Jan/17/01	Aug/23/01	167.0
60 Demonstration Lot 1200 L (3 runs; 399 kg)	Apr/01/02 ?	Jun/21/02	399.0
65 Process Transfer(i) 600L U.K. Site (3X 83 kg= 249kg)	Apr/19/01	May/18/01	249.0
Process Transfer (ii) 600L U.K. (2x 83kg= 166 kg)	Jun/27/01	Jul/24/01	166.0
Bio Batch UK	Sep/13/01	Oct/02/01	83.0
Batch Analysis, 2 lots; 2x 83 kg	Sep/05/01	Sept/27/01	166.0
Demo Batch 1 UK; (1 lot, 3 runs= 333 kg)	Apr/04/02	May/03/02	333.0
1200L Validation Runs (3 Lots, 3 Runs ea; 1197 kg)	Jun/05/02	Aug/28/02	1200.0
Launch		1Q2003	
Total Bulk Drug Usage			5823.90

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Schedule C

**Bulk Drug Cost Status**

	<b>Current Average Cost (000)</b>	<b>Projected Commercial Cost (000)</b>
Materials	3.7	1.3
Labor/Equipment	2.4	1.05
Process Support	0.4	.15
<b>Total</b>	<b>6.5</b>	<b>2.5</b>

<b>Event</b>	<b>Year</b>	<b>Project Average Cost/Kilo</b>		
		<b>DDC</b>	<b>Actual/Projected</b>	
DDC	97	150	150	
	98	30	30	A
Phase IIb	99	10	10	A
Phase III start	00	7.5	6.7	A
	01	5.0	5.0	P
Filing	02	4.0	4.0	P
Launch	03	2.5	2.5	P
Dose Projection		150mg/Day	150mg/Day	
Cost/Dose/Day Bottle		\$0.4218/Day	\$0.4218/Day	
Cost/Dose/Day Blister		\$0.5702/Day	\$0.5702/Day	

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ABBT205010



### H.3 PARD/IDC

An immediate release 150 mg formulation has been selected for commercial development of ABT 773. The formulation was reduced in size from the original 300 mg tablet previously targeted for development. The formula and process will be global with respect the excipients and an integrated scale up program with the IDC will assure that a single formula/process (with common packages) will be used throughout the world. The CMC working group continues to review needs on the bulk drug for clinical use and process development as the program develops. Common specifications for the bulk drug substance and the formulation remain a goal of the CMC development group.

### H.4 Manufacturing

ABT-773 tablets will be manufactured in AP16 for PPD domestic supply, and as a back-up facility for AI supply. Queenborough, UK will manufacture for AI supply, including Japan. There will be a common, global formula (0.3g tablet weight, with pale pink coating ). The only possible exception will be if we need to develop different codes of bulk drug for PPD and AI.

The manufacturing process is a conventional tableting process. In AP16, ABT-773 will be granulated in the 1200L Gral, in 3 runs, then blended (75 cuft), compressed and coated (60" Accelacoater) as 150mg tablets. In the UK, ABT-773 will be granulated in the 600L TK Fielder, in the 3 runs, then blended and coated as 150mg tablets. The Japanese product will be manufactured with the same granule, to a lower compression weight, if Japan proceeds with 100mg tablets. This strength is yet to be determined. Capacity reviews at both plants indicate that there is sufficient capacity, including upside demand. The tablets will be packaged into 30# bottles, and peelable blister (Hospital Unit Dose) and push-through blister (compliance pac)

### H.5 Patent Issues

U.S. Patent 5,866,549 claiming ABT-773 and its analogs issued on February 2, 1999. The patent will expire on September 4, 2016. Three divisional applications claiming related compounds in the series are pending prosecution in the United States Patent and Trademark Office. The patent applications corresponding to the issued patent and pending patent applications have been filed in more than forty countries outside the US, thus providing extensive worldwide patent protection for the compound

## I. Non-Clinical

### I.1 Non-Clinical SWOT Analysis

Strengths, weakness, opportunities and threats regarding the non-clinical program for ABT-773 are discussed below:

Table L1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<p>All key toxicology studies have been initiated or completed.</p> <p>ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Erm AM and Mef phenotypes; it does not induce MLS<sub>B</sub> (macrolides, lincosamides and streptogramin B) resistance.</p>	<p>Complete Tox package for NDA early on.</p> <p>Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.</p>
Weaknesses	<p>Tox: Relatively small safety margins between the no-effect level exposures and clinical exposure.</p> <p>Micro: Pharmacokinetic profile based on traditional profiles, may not support the 150mg dose.</p> <p><i>H. Flu</i> MIC 2-4 is a high MIC to achieve by blood levels.</p>	<p>Safety data is available from clinical studies.</p> <p>Ribosome kinetics are now being studied as a means of providing crucial support to our decision to proceed with 150 mg. A plan has been established to devise a mechanistic rationale for the 150 mg program that goes beyond the traditional two-factor paradigm i.e. concentration &amp; MIC and establishes this concept as the new in vitro paradigm to predict efficacy.</p> <p>Demonstrate clinical activity in <i>H. flu</i> and use tissue level data if available.</p>
Opportunities	<p>Micro: Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes</p>	<p>Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.</p>
Threats	<p>Testicular effects and impaired fertility in the rat Segment I study.</p>	<p>Fertility evaluation should be included in the clinical program.</p>

## 1.2 Toxicology

All key toxicology studies for ABT-773 have been initiated or completed. All acute and genetic toxicity studies, two-week toxicity studies in rat and monkey, one-month toxicity studies in rat and monkey, a three-month study in rat, and embryonic and fetal developmental (Segment II) studies have been completed. A three-month study in monkey, a juvenile toxicity study in rat, a fertility and early embryonic development (Segment I) study in rat, a peri- and postnatal (Segment III) study in rat and an antigenicity study in guinea pig are ongoing.

In rats, increased mortality, decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, lung, testes and epididymides were observed at dosages of 180 and 160 mg/kg/day in the one-month and three-month study, respectively. Mild and reversible toxicity of these organ systems was seen at 60 mg/kg/day. The no-toxic-effect level (NTEL) in the three-month rat study was 20 mg/kg/day ( $AUC = 11-25 \mu\text{g}\cdot\text{hr}/\text{ml}$ ). The mean plasma exposure of ABT-773 in humans is expected to be 2-5  $\mu\text{g}\cdot\text{hr}/\text{ml}$  (150-300 mg/day dose) and thus the NTEL in animals are approximately 2-13 times higher than anticipated human exposures.

In monkeys, emesis was observed in a dose-related manner. Decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, bone marrow and lymphoid tissues were observed at a dosage of 200/140 mg/kg/day in the one-month study. Preliminary data showed that liver toxicity was also observed at dosages of 50 and 100 mg/kg/day in the three-month study. The no-toxic-effect level (NTEL) in the three-month monkey study was 25 mg/kg/day ( $AUC = 7-10 \mu\text{g}\cdot\text{hr}/\text{ml}$ ); exposures at this dosage are approximately 1.5-5 times higher than anticipated human exposures.

Embryonic and fetal developmental studies conducted showed no fetal malformation at dosages up to 80 mg/kg/day in rats and 100 mg/kg/day in rabbits. In an ongoing fertility and early embryonic development study, preliminary data showed adverse effects on fertility at dosages of 60 and 180 mg/kg/day. Recovery of this effect on fertility was seen at 60 mg/kg/day, but not at 180 mg/kg/day. This finding agrees with the testicular effects seen in the three-month rat study. Clinical implications of this finding is not known, although similar findings have been reported with other macrolides. Preliminary data of the peri- and postnatal study showed decreased pup growth and development at 80 mg/kg/day; these effects were believed to be secondary to reduced weight gain of dams during gestation.

Genetic toxicology studies conducted with ABT-773 included Ames assay, mouse lymphoma assay, *in vitro* cytogenetics assay and *in vivo* mouse micronucleus assay. ABT-773 was not found to be genotoxic in any of these assays.

New impurities, not covered by the toxicology lot used for three-month studies, have been generated. Acute toxicity, genotoxicity and bioavailability studies are being conducted with these impurities to qualify their use in the clinical trials. Longer term toxicology testing will be done when the impurity profile for ABT-773 is determined (NDA runs).

### L3 Metabolism

Studies of the oral or intravenous single dose pharmacokinetics of ABT-773 have been performed in the rat, mouse, dog and monkey following single doses. These data suggested ABT-773 may possess a balanced pharmacokinetic profile similar to that of clarithromycin. ABT-773 exhibits sufficient plasma concentrations and tissue distribution to provide effective treatment *in vivo* for bacterial infections of upper and lower respiratory tract. The data from the study in dogs indicate that ABT-773 has a favorable oral pharmacokinetic profile with 51.3% absolute bioavailability from a simple capsule formulation and low animal-to-animal variability. ABT-773 has a half-life similar to that of clarithromycin in dogs (4.1 and 5.4 hrs, respectively), with a  $C_{max}$  of 0.88  $\mu\text{g/mL}$  following an oral dose of 5 mg/kg.

[ $^{14}\text{C}$ ] ABT-773 was found to undergo NADPH-dependent metabolism by liver microsomes from mouse, rat, dog, monkey and humans with wide interspecies variability in the rates of metabolism with monkey and rat exhibiting highest and lowest rates of metabolism, respectively. In all cases the major metabolite formed was an *N*-desmethyl derivative of ABT-773 (M-1). ABT-773 is rapidly cleared in rats after intravenous and oral administration and in dogs by oral administration. For both species, excretion is primarily by the liver with only a small fraction of the dose eliminated in the urine.

The *in vitro* studies across five species including man, suggest that ABT-773 shows a drug-concentration dependent decrease in protein binding. In man, for plasma concentrations above 3 mg/mL, plasma protein binding decreases with increasing total drug concentrations, presumably due to the saturation of the plasma binding sites. Because plasma concentrations of ABT-773 in humans are unlikely to exceed 2 mg/mL at clinically-relevant doses, the concentration dependence is not clinically important. In human plasma, [ $^{14}\text{C}$ ] ABT-773 has a greater affinity for  $\alpha_1$ -acid glycoprotein (AAG) than for human serum albumin (HSA), and plasma protein binding at concentrations of 0.1 to 3  $\mu\text{g/mL}$  was 95.5-95.6%.

ABT-773 is metabolized by human liver microsomes via CYP3A4. The drug also appears to be an inhibitor of CYP3A4 metabolism *in vitro*. The  $IC_{50}$  values obtained for the inhibition of CYP3A4-dependent metabolisms were in the same range as the total steady state peak plasma concentrations of ABT-773 (0.45 - 1.92  $\mu\text{g/mL}$ ) after 200-500 mg BID doses in humans. This indicates the potential for ABT-773 to inhibit the *in vivo* metabolism of coadministered drugs metabolized via CYP3A4.

#### **I.4 Animal Safety Pharmacology**

The pharmacology studies showed that ABT-773 has mild sedative actions with only modest, if any effects on other CNS, CV and/or GI functions at therapeutic to super therapeutic doses/plasma concentrations. These results indicate a minimal risk for marked adverse effects of this compound in clinical studies.

In *in vitro* cellular electrophysiologic studies, supratherapeutic concentrations of ABT-773 (at concentrations 10- and 100-fold above anticipated clinical therapeutic plasma levels) prolong the action potential duration of canine cardiac Purkinje fibers superfused with physiologic salt solutions. These *in vitro* studies likely overestimate the electrophysiologic effects of ABT-773 *in vivo* due to the extensive plasma protein binding of ABT-773. Prolongation of the Purkinje fiber action potential duration *in vitro* is dramatically reduced in the presence of plasma proteins; in the presence of 50% plasma, the dose-response curve for prolongation is shifted rightward, with significant prolongation observed only at 100-fold above the anticipated plasma levels of ABT-773.

When studied in the absence of plasma, the extent of action potential prolongation with ABT-773 is comparable to erythromycin, clarithromycin, and levofloxacin, and less than that of moxifloxacin when compared on the basis of plasma concentration multiples. Studies of M-1, the principal metabolite of ABT-773, demonstrate minimal effects on repolarization and only at high metabolite concentrations (100-fold excess of those found at clinically efficacious concentrations). An *in vivo* toxicology study with non-human primates reveals no significant prolongation of the QTc interval despite long-term exposure to supratherapeutic plasma levels of ABT-773.

#### **I.5 Microbiology**

In the past year, various external investigators have confirmed and expanded the early pre-clinical studies done at Abbott. The activity of ABT-773 against current respiratory tract

isolates including *S. pneumoniae* (macrolide susceptible and resistant), *H. influenzae* and *M. catarrhalis* was examined. An antibiotic surveillance study done by the University of Iowa found the MIC<sub>90</sub> of ABT-773 for *S. pneumoniae* (n=1601) was 0.03 µg/ml. Furthermore, the MIC<sub>90</sub> against low and high level macrolide resistant strains was 0.12 µg/ml. The highest ABT-773 MIC found in the study was 0.5 µg/ml (n=3). The activity of ABT-773 was found to be equivalent to azithromycin and superior to clarithromycin against *H. influenzae* and the ketolide was extremely potent against *M. catarrhalis*. Additional studies done by several other investigators confirmed these findings for respiratory pathogens. Kill kinetic studies with fastidious respiratory pathogens confirmed the bactericidal activity of ABT-773. The ketolide also showed extended post antibiotic effect compared to other macrolides for *S. pneumoniae* and *H. influenzae*.

Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes. Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.

ABT-773 demonstrates *in vivo* efficacy equal or superior to available clinical therapeutics in animal studies against the most prevalent respiratory pathogens including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Once daily (QD) therapy was as effective as twice daily (BID) therapy in treatment of rat pulmonary infections caused by *H. influenzae* and *S. pneumoniae*. ABT-773 also demonstrated efficacy against macrolide and penicillin resistant strains of *Streptococcus pneumoniae*. Efficacy was demonstrated against infections of salient anatomical locations including systemic (septic), inner ear (bullae), pulmonary, and skin abscess suggesting that ABT-773 penetrates into pulmonary tissue and intracellular locations while maintaining activity.

## **Addenda**

- 1.0 Target Product Label**
- 2.0 Clinical Trial Program**
  - 2.1 Clinical Trials (Gantt Chart)**
- 3.0 Chemistry, Manufacturing and Controls**
  - 3.1 Milestones SPD/PPD Chemical Sciences Milestones (Gantt Chart)**
  - 3.2 PARD Milestones (Gantt Chart)**
- 4.0 Non-Clinical**
  - 4.1 Animal Toxicology and Metabolism Milestones (Gantt Chart)**
- 5.0 Project History**
  - 5.1 Expert Strategic Review Process - Summaries**
  - 5.2 Milestones**
  - 5.3 Highlights re: NCE**
  - 5.4 Historical Changes to ABT-XXX Target Product Profile**

## Appendix 1

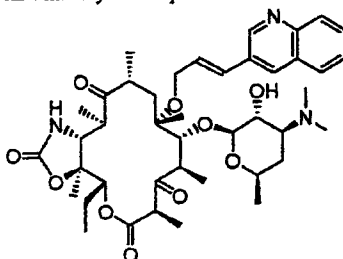
## Target Product Label

**ERADICATE® Filmtab®**

(eradomycin tablets)

**DESCRIPTION**

Eradomycin is a semi-synthetic ketolide antibiotic. Chemically, it is 11-amino-11-deoxy-3-oxo-5-O-desosaminyl-6-O-[3'-(3"-quinoliny)-2'-propenyl] erythronolide.<sup>1</sup> A 11,12-cyclic carbamate. The molecular formula is  $C_{42}H_{58}N_3O_{10}$ , and the molecular weight is 765.94<sup>2</sup>. The structural formula is:



ERADOMYCIN is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol,

ethanol, and acetonitrile, and practically insoluble in water<sup>3</sup>.

ERADOMYCIN is available as immediate release tablets.

Each ovaloid film-coated ABT-773 tablet contains 150 mg of ABT-773 and the following inactive ingredients:

Cellulose, Microcrystalline, NF  
Croscarmellose, Sodium, NF  
Hydroxypropyl Cellulose NF  
Magnesium Stearate, NF, Impalpable Powder  
Silicon Dioxide, Colloidal, NF  
Sodium Starch Glycolate, NF Powder  
Starch, Pregelatinized, NF

**Plus- coating solution (STILL BEING DEFINED):**

iron oxides, hydroxypropyl methylcellulose, Polyethylene Glycol, Titanium Dioxide, sorbic acid?<sup>4</sup>.

<u>Study #</u>	<u>Comment</u>	<u>Start</u>	<u>End</u>	<u>Investigator/Contact</u>
<sup>1</sup> NA	Confirm chemical name (IUPAC)			Z. Ma
<sup>2</sup> NA	Confirmed			Z. Ma
<sup>3</sup> NA	Confirmed			Z. Ma
<sup>4</sup> NA	Info correct, how specific is required?			R. Schilling



## CLINICAL PHARMACOLOGY

ERADOMYCIN is rapidly absorbed from the gastrointestinal tract after oral administration<sup>5</sup>. The absolute bioavailability of 150-mg ERADOMYCIN tablets was approximately 77%<sup>6, 7, 8</sup>. Food effects neither the rate nor extent of ERADOMYCIN absorption. Therefore, ERADOMYCIN tablets may be given without regard to food<sup>9</sup>.

In fasting healthy human subjects, peak serum concentrations were attained within 3 hours after oral dosing<sup>10, 11</sup>. Steady-state peak serum ERADOMYCIN concentrations were attained in 3 to 4 days<sup>12</sup> and were approximately 1 µg/mL<sup>13</sup> with a 150-mg dose administered every 24 hours. The pharmacokinetics of ERADOMYCIN are non-linear around the recommended dose of 150 mg administered once daily<sup>14, 15</sup>. Typical pharmacokinetic parameters of ERADOMYCIN are shown in the following table.

Error! Bookmark not defined.PHARMACOKINETIC PARAMETERS  
(after 150 mg q 24 h)

$T_{max}$ <sup>16</sup> (h)	$T_{1/2}$ <sup>17</sup> (h)	$C_{max}$ <sup>18</sup> (ng/ml)	$C_{min}$ <sup>19</sup> (ng/ml)	AUC <sup>20</sup> (ng·h/ml)
2.7 ± 0.6		855 ± 366	29 ± 13	5934 ± 2623

After a 150-mg tablet every 24 hours, approximately 7%<sup>21</sup> of the dose is excreted in the urine as ERADOMYCIN. [No metabolite info presented; may have to defend]. [Does CYP3A have to be mentioned?]. The elimination half-life of ERADOMYCIN was about 6 to 8 hours<sup>22</sup> with 150 mg administered every 24 hours.

The steady-state concentrations of ERADOMYCIN in subjects with impaired hepatic function did not differ from those in normal subjects<sup>23</sup>; the steady-state concentrations of ERADOMYCIN in subjects with impaired renal function did not differ from those in normal subjects<sup>24</sup>. [Will conduct study in elderly<sup>25</sup>; will add comments about

<sup>5</sup> M00-AAA	Definitive biostudy
<sup>6</sup> M00-BBB	Single ascending IV, final, multiple rising dose + p.o.; assumes p.o. does not have to be final scale for 8/00 start
<sup>7</sup> 100097	
<sup>8</sup> 100098	
<sup>9</sup> M00-AAA	To be part of definitive biostudy
<sup>10</sup> M97-716	3 hrs based on 716
<sup>11</sup> M00-AAA	Confirmed with definitive biostudy
<sup>12</sup> M99-024	3-4 days based on 024 study; repeat only if diff. between 024 and 10-75L scaleup (M99-129)
<sup>13</sup> M99-024	024 showed 1 mcg/ml; repeat only if diff. between 024 and 10-75L scaleup (M99-129) '1'.
<sup>14</sup> M99-018	Quantify non-linearity from study
<sup>15</sup> M00-CCC	150/300/600 mg single comparative study
<sup>16</sup> M99-016	If done, 018 would not be used; could also use M99-119 caucasian section
<sup>17</sup> M99-016	Placeholder study; replace with M00-AAA
<sup>18</sup> M99-016	Placeholder study; replace with M00-AAA
<sup>19</sup> M99-016	Placeholder study; replace with M00-AAA
<sup>20</sup> M99-016	Placeholder study; replace with M00-AAA
<sup>21</sup> M00-DDD	C14 study, if low number (<20%), multiple dose will not be required
<sup>22</sup> M99-024	6-8 hours based on 024 study; will also be based on M00-AAA
<sup>23</sup> M99-126	Protocol finished
<sup>24</sup> M00-FFF	Low urine excretion will not require results of C14;
<sup>25</sup> M01-AAA	Study in elderly; need final dosage form/dose

gender subanalyses but no specific studies]

Do we need adolescent study/section in label?

**Distribution:**

ERADOMYCIN distributes readily into body tissues and fluids. Volume of distribution?<sup>26</sup> Rapid distribution of eradomycin into tissues results in higher eradomycin concentrations in most target tissues than in serum (see table below) [will use either tissue and serum values or only ratios, whichever looks more favorable].

**Error! Bookmark not defined.CONCENTRATION**  
(after 150 mg q 24 h)

Tissue Type	Tissue (µg/g)	Serum (µg/mL)	T:S Ratio (µg/mL)
Tonsil <sup>27</sup>	X.X	X.X	X.X
Lung <sup>28, 29</sup>	X.X	X.X	X.X
Epithelial Lining Fluid <sup>30, 31</sup>	X.X	X.X	X.X
Alveolar Macrophage <sup>32, 33</sup>	X.X	X.X	X.X
White Blood Cells <sup>34</sup>	X.X	X.X	X.X
Sinus Mucosa <sup>35</sup>	X.X	X.X	X.X
Cerebral Spinal Fluid <sup>36</sup>	X.X	X.X	X.X
Bronchial Mucosa <sup>37</sup>	X.X	X.X	X.X
Sputum <sup>38</sup>	X.X	X.X	X.X

- <sup>26</sup> M00-BBB Absolute bioavailability study
- <sup>27</sup> M99-142 Conte study; all raw data must be sent to Abbott, will forward to FDA (10009)
- <sup>28</sup> M99-142
- <sup>29</sup> M99-007 Gottfried to execute; contact Gottfried for proposal
- <sup>30</sup> M99-142 Conte study
- <sup>31</sup> M99-007
- <sup>32</sup> M99-142 Conte study
- <sup>33</sup> M99-007
- <sup>34</sup> M99-105 Samples being reanalyzed, orig. results relatively low
- <sup>35</sup> TBD; not sure if pursuing
- <sup>36</sup> M99-142 Conte study
- <sup>37</sup> TBD; not sure if pursuing
- <sup>38</sup> TBD; not sure if pursuing, ELF is better fluid

## Microbiology:

ERADOMYCIN is a ketolide with concentration-dependent, bactericidal *in-vitro* activity against a wide range of aerobic and anaerobic gram-negative, gram-positive, and atypical microorganisms. ERADOMYCIN exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of bacterial protein synthesis<sup>39 40 41 42</sup>. ABT-773 binds to the ribosome rapidly, completely, and irreversibly<sup>43</sup>. It appears that these ribosome-binding properties contribute to enhanced activity and lower selection of resistant mutants of gram-positive bacteria relative to other agents that act via the ribosome<sup>44 45 46 47</sup>. Eradomycin exhibits an in-vitro post-antibiotic effect (PAE), defined as the ability of an agent to sustain antimicrobial action after drug concentrations have fallen below the MIC.<sup>48 49 50</sup>

The mechanism of action of ketolides including eradomycin is different from that of penicillins, cephalosporins, quinolones, aminoglycosides, and tetracyclines<sup>51</sup>. Therefore, ERADOMYCIN may be active against pathogens that are resistant to these antibiotics<sup>52 53 54 55</sup>. There is no cross-resistance between ERADOMYCIN and the mentioned classes of antibiotics<sup>56</sup>.

Macrolide resistance occurs principally by two main mechanisms of resistance. Production of ribosomal methylases, either inducible or constitutive, alters the ribosomal target inhibiting macrolide binding; an efflux mechanism pumps the antibiotic from within the microorganism. ERADOMYCIN has been shown in streptococcus to bind to methylated ribosomes<sup>57 58</sup>, to not induce methylase resistance<sup>59 60</sup>, and to bypass the efflux pump<sup>61 62</sup>. Thus ERADOMYCIN is active against macrolide resistant streptococci<sup>63 64 65</sup>.

Resistance to ERADOMYCIN in vitro develops slowly<sup>66</sup>. Resistance to ERADOMYCIN in vitro occurs at a

<sup>39</sup> <u>99040</u>	Capobianco
<sup>40</sup> <u>99017</u>	Zhong
<sup>41</sup> <u>99032</u>	Zhong
<sup>42</sup> <u>100077</u>	Zhong
<sup>43</sup> <u>99040</u>	
<sup>44</sup> <u>99058</u>	Liebowitz study (serial dilution)
<sup>45</sup> <u>100079</u>	Nilius, will be at ICAAC00
<sup>46</sup> <u>100027</u>	Pendland
<sup>47</sup> <u>100048</u>	
<sup>48</sup> <u>99001</u>	Appelbaum; partial ICAAC99, ICAAC00
<sup>49</sup> <u>100078</u>	Ramer
<sup>50</sup> <u>99014</u>	Dubois
<sup>51</sup>	Scientifically accepted; provide literature references
<sup>52</sup> <u>99051</u>	
<sup>53</sup> <u>99030</u>	
<sup>54</sup> <u>99038</u>	
<sup>55</sup> <u>99042</u>	
<sup>56</sup>	99051, 99030, 99038, 99042
<sup>57</sup> <u>99040</u>	Zhong mechanism of action reference
<sup>58</sup> <u>99071</u>	Mankin
<sup>59</sup> <u>99040</u>	
<sup>60</sup> <u>99038</u>	Shortridge
<sup>61</sup> <u>99040</u>	
<sup>62</sup> <u>99038</u>	
<sup>63</sup> <u>99038</u>	Multiple in-vitro studies
<sup>64</sup> <u>99051</u>	
<sup>65</sup> <u>99030</u>	
<sup>66</sup>	99058, 100027, 100079

general frequency of between  $1 \times 10^{-2}$  to  $10^{-67}$ .

ERADOMYCIN has been shown to be active against most strains of the following microorganisms both *in-vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

**Aerobic Gram-Positive Microorganisms**

*Staphylococcus aureus* (methicillin-susceptible strains; macrolide inducibly resistant and efflux strains)

*Staphylococcus epidermidis* (methicillin-susceptible strains)

*Streptococcus pneumoniae* (including penicillin-susceptible, intermediate and resistant strains; macrolide susceptible, intermediate and resistant strains; quinolone susceptible, intermediate and resistant strains)

*Streptococcus pyogenes* including macrolide susceptible, intermediate and resistant strains;

**Aerobic Gram-Negative Microorganisms**

*Haemophilus influenzae* (including beta-lactamase producing strains and beta-lactamase negative ampicillin resistant (BLNAR) strains)

*Haemophilus parainfluenzae* (including beta-lactamase producing strains)

*Moraxella catarrhalis* (including beta-lactamase producing strains)

**Other Microorganisms**

*Mycoplasma pneumoniae*

*Chlamydia pneumoniae* (TWAR)

*Legionella pneumophila*

The following *in vitro* data are available, but their clinical significance is unknown.

Eradomycin exhibits *in-vitro* minimum inhibitory concentrations (MICs) of  $\leq 2$   $\mu\text{g/ml}$  against most ( $\geq 90\%$ ) strains of the following bacteria; however, the safety and effectiveness of eradomycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

**Aerobic Gram-positive Microorganisms**

*Streptococcus agalactiae*

Streptococci (Groups C, F, G)

Coagulase negative staphylococci (methicillin susceptible)

Viridans group streptococci

***Corynebacterium jeikeium***

*Corynebacterium spp.*

***Listeria monocytogenes***

**Aerobic Gram-negative Microorganisms*****Bordetella pertussis****Legionella pneumophila**Neisseria meningitidis**Neisseria gonorrhoeae* (including penicillin resistant and quinolone resistant strains)**Anaerobic Gram-positive Microorganisms*****Peptostreptococci****Propionibacterium acnes**Clostridium difficile**Clostridium perfringens***Anaerobic Gram-negative Microorganisms***Bacterioides spp.**Porphyromonas spp.**Prevotella spp.****Dilution Techniques***

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erandomycin powder. The MIC values obtained should be interpreted according to the following criteria:

**For testing non-fastidious aerobic organisms**

MIC (µg/mL)	Interpretation
<2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

**For testing *Haemophilus spp.*<sup>a</sup>**

MIC (µg/mL)	Interpretation
≤4.0	Susceptible (S)
8.0	Intermediate (I)
≥16.0	Resistant (R)

<sup>a</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus spp.* using *Haemophilus* Test Medium (HTM).<sup>1</sup>

**For testing *Streptococcus spp.* including *Streptococcus pneumoniae*<sup>b</sup>**

MIC (mcg/mL)	Interpretation
--------------	----------------

≤0.5	Susceptible (S)
1.0	Intermediate (I)
≥2.0	Resistant (R)

<sup>b</sup> These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.<sup>1</sup>

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control bacterial strains to control the technical aspects of the laboratory procedures. Standard eradomycin powder should provide the following MICs with these quality control strains:

Microorganisms	MIC Ranges <sup>ca</sup> (µg/mL):
<i>Staphylococcus aureus</i> ATCC 29213	0.016-0.12
<i>Haemophilus influenzae</i> <sup>c</sup> ATCC 49247	1.0-4.0
<i>Streptococcus pneumoniae</i> <sup>d</sup> ATCC 49619	0.002-0.016

<sup>c</sup> This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM.<sup>1</sup>

<sup>d</sup> This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.<sup>1</sup>

#### **Diffusion Techniques**

Quantitative methods that require measurement of zone diameters of growth inhibition provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with eradomycin (equivalent to 15-mcg eradomycin) to test the susceptibility of bacteria to eradomycin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a eradomycin disk (equivalent to 15-mcg eradomycin) should be interpreted according to the following criteria.

#### **For testing non-fastidious aerobic bacteria:**

Zone Diameter (mm)	Interpretation
≥23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

#### **For testing *Haemophilus spp.*<sup>e</sup>:**

Zone Diameter (mm)	Interpretation <sup>f</sup>
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<sup>68</sup> 99044

NCCLS will also have impact

≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant (R)

<sup>a</sup> This zone diameter standard is applicable only to tests with *Haemophilus* spp. using HTM.<sup>2</sup>

For testing *Streptococcus* spp. including *Streptococcus pneumoniae* <sup>d</sup>:

Zone Diameter (mm)	Interpretation <sup>f</sup>
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

<sup>d</sup> These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.<sup>2</sup>

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product)

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the eradomycin equivalent to a 15-mcg eradomycin disk should provide the following zone diameters in these laboratory quality control strains:

#### Zone Diameter Ranges

*Staphylococcus aureus* ATCC 25923 XXXXXmm

*Haemophilus influenzae*<sup>b</sup> ATCC 49247 XXXXXmm

*Streptococcus pneumoniae*<sup>c</sup> ATCC 49619 XXXXXmm

<sup>b</sup> This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM.<sup>2</sup>

<sup>c</sup> This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.<sup>2</sup>

Summaries of susceptibility interpretive criteria and acceptable quality control ranges for eradomycin to be used for validation of susceptibility test results can be shown in the following tables:

#### Susceptibility Interpretive Criteria for Eradomycin

Microorganisms	MIC (µg/mL)			Disk Diffusion (mm)		
	S	I	R	S	I	R
Aerobic Non-Fastidious	≤2	4	≥8	≥23	20-22	≤19
<i>Haemophilus</i> spp.	≤4	8	≥16	≥16	13-15	≤12
<i>Streptococcus</i> spp. including <i>S. pneumoniae</i>	≤0.5	1	≥2	≥20	17-19	≤16

S = susceptible, I = intermediate, R = resistant

Acceptable Quality Control Ranges for Erythromycin To Be Used In Validation of Susceptibility Test Results

Quality Control Strain	MIC (mcg/mL)	Disk Diffusion (mm)
<i>Streptococcus pneumoniae</i> ATCC 49619	0.002-0.016	XXXXX
<i>Haemophilus influenzae</i> ATCC 49247	0.03-0.12	XXXXXX
<i>Staphylococcus aureus</i> ATCC 25913	0.016-0.12	Not Applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	XXXXX

#### INDICATIONS AND USAGE

ERADOMYCIN Filmtab tablets are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

##### Adults:

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes* (The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. ERADOMYCIN is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of ERADOMYCIN in the subsequent prevention of rheumatic fever are not available at present.)

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae* or *Streptococcus pneumoniae*

Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Chlamydia pneumoniae* (TWAR)

In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended. (For information on development of resistance see Microbiology section.)

#### CONTRAINDICATIONS

ERADOMYCIN is contraindicated for patients with a known hypersensitivity to ERADOMYCIN or any macrolide or ketolide antibiotics.

#### WARNINGS

ERADOMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF <sup>69</sup> <sup>70</sup> <sup>71</sup>. (See PRECAUTIONS - Pregnancy.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ERADOMYCIN, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

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<sup>69</sup> Seg 1  
<sup>70</sup> Seg 2  
<sup>71</sup> Seg 3



Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

## PRECAUTIONS

### General:

ERADOMYCIN is principally excreted via the liver. ERADOMYCIN may be administered without dosage adjustment to patients with hepatic impairment<sup>72</sup> and normal renal function<sup>73</sup>. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

*Information to Patients:* ERADOMYCIN tablets can be taken with or without food<sup>74</sup>.

### Drug Interactions:

To be written pending outcome of drug interaction studies.

### Planned drug interaction studies:

- 1) Ketoconazole<sup>75</sup>
- 2) Impact of rifampin on 773<sup>76</sup>
- 3) Impact of 773 on oral contraceptives<sup>77</sup>
- 4) Impact of 773 on theophylline<sup>78</sup>
- 5) Digoxin<sup>79</sup>
- 6) Impact of 773 on midazolam<sup>80</sup>
- 7) Nifedipine<sup>81</sup>
- 8) Statin<sup>82</sup>
- 9) Warfarin<sup>83</sup>
- 10) Carbamazepine<sup>84</sup>
- 11) Cyclosporin<sup>85</sup>
- 12) Loratadine<sup>86</sup>

Potentially add general CYP3A statements rather than individually doing studies on individual drugs

### Mutagenesis, Carcinogenesis, Impairment of Fertility:

<sup>72</sup> M99-126	Hepatic study
<sup>73</sup> M00-154	Renal study
<sup>74</sup> M00-AAA	Final biostudy
<sup>75</sup> 100099	
<sup>76</sup> 100090	M00-156
<sup>77</sup> 100100	M99-128
<sup>78</sup> 100101	M99-139
<sup>79</sup> 100102	
<sup>80</sup> 100089	M00-155; If does not increase midazolam conc (not likely), no need to do 100103 or 100104
<sup>81</sup> 100103	Pending
<sup>82</sup> 100104	Pending
<sup>83</sup> 100105	
<sup>84</sup> 100107	
<sup>85</sup> 100108	
<sup>86</sup> 100109	

The following *in vitro* mutagenicity tests have been conducted with ERADOMYCIN:

In Vitro Cytogenetics Assay in Human Lymphocytes<sup>87</sup>  
 Mouse Lymphoma Assay<sup>88</sup>  
 Mouse Micronucleus Test<sup>89</sup>  
 Bacterial Reverse-Mutation Test (Ames Test)<sup>90</sup>.

All tests had negative results.

Fertility and reproductive studies have shown that daily doses of up to ? mg/kg/day (X times the recommended maximum human dose based on mg/m<sup>2</sup>) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after ? mg/kg/day were X times the human serum levels.<sup>91 92 93</sup>

In rabbits, no treatment-related effects on fetal viability or growth were observed.<sup>94</sup>

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ERADOMYCIN.

*Pregnancy:* Category B or C<sup>95</sup>.

X number teratogenicity studies in rats (three with oral doses and one with intravenous doses up to X mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to X mg/kg/day (approximately X times the recommended maximum human dose based on mg/m<sup>2</sup>) or intravenous doses of X mg/kg/day administered during gestation days X to X failed to demonstrate any teratogenicity from ERADOMYCIN. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of X mg/kg/day administered during gestation days X to X. Plasma levels after X mg/kg/day were X times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of X mg/kg/day (X and X times the recommended maximum human dose based on mg/m<sup>2</sup>, respectively) during gestation days X to X. Cleft palate was also seen at X mg/kg/day. The X mg/kg/day exposure resulted in plasma levels X times the human serum levels. In monkeys, an oral dose X mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m<sup>2</sup>) produced fetal growth retardation at plasma levels that were X times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. ERADOMYCIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

*Nursing Mothers*<sup>96</sup>:

It is not known whether ERADOMYCIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ERADOMYCIN is administered to a nursing woman. It is known that ERADOMYCIN is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

<sup>87</sup> 100111  
<sup>88</sup> 100114  
<sup>89</sup> 100116  
<sup>90</sup> 100117  
<sup>91</sup> 100118 Seg 1  
<sup>92</sup> 100120 Seg 2 (rats)  
<sup>93</sup> 100119 Seg 3  
<sup>94</sup> 100106  
<sup>95</sup> 100119 Seg 3  
<sup>96</sup> 100110 Study TBD

**Pediatric Use:**

The safety and effectiveness of ERADOMYCIN in pediatric patients have not been established

[If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.]

**Geriatric Use<sup>97</sup>:**

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 150 mg every 24 hours, the maximum serum concentrations and area under the curves of ERADOMYCIN were increased? compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

[If clinical studies did not include sufficient numbers (100) of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection of PRECAUTIONS shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."]

**ADVERSE REACTIONS**

The majority of side effects observed in clinical trials were of a mild and transient nature.

The most frequently reported events in adults were diarrhea (X%), nausea (X%), abnormal taste (X%), dyspepsia (X%), abdominal pain/discomfort (X%), and headache (X%)<sup>98</sup>. Most of these events were described as mild or moderate in severity. Of the reported adverse events, only X% was described as severe.

In sinusitis studies conducted in adults comparing ERADOMYCIN to amoxicillin/clavulanic acid, there were fewer adverse events involving the digestive system in ERADOMYCIN-treated patients compared to amox/clav-treated patients (X% vs X%; p<0.01). Twenty percent of amoxicillin/clavulanic acid-treated patients discontinued therapy due to adverse events compared to 4% of ERADOMYCIN-treated patients.

Taste/GI comparable to Zithromax in AECB study?

**Changes in Laboratory Values<sup>99</sup>:** Changes in laboratory values with possible clinical significance were as follows:

Hepatic - elevated SGPT (ALT) < X%; SGOT (AST) < X%; GGT < X%; alkaline phosphatase < X%; LDH < X%; total bilirubin < X%

Hematologic - decreased WBC < X%; elevated prothrombin time X%

Renal - elevated BUN X%; elevated serum creatinine < X%

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

**DOSAGE AND ADMINISTRATION**

ERADOMYCIN® Filmtab® (ERADOMYCIN tablets may be given with or without food<sup>100</sup>.

<sup>97</sup> M01-AAA

Study in elderly; need final dosage form/dose

<sup>98</sup>

Phase III studies

<sup>99</sup>

<sup>100</sup> 100064

M97-716

**Error! Bookmark not defined.ADULT DOSAGE GUIDELINES**

<b>Infection</b>	<b>Dosage (q24h)</b>	<b>Normal Duration (days)</b>
Pharyngitis/Tonsillitis	150 mg	5 days
Acute bacterial sinusitis	150 mg	10 days
Acute exacerbation of chronic bronchitis:	150 mg	5 days
Community-acquired pneumonia including <i>mycoplasma</i> , <i>chlamydia</i> and <i>legionella</i>	150 mg	7-10 days

ERADOMYCIN may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function<sup>101 102</sup>.

**HOW SUPPLIED**

ERADOMYCIN® Filmtab® (ERADOMYCIN tablets) are supplied as COLOR oval film-coated tablets containing 150 mg of ERADOMYCIN imprinted (on one side) in COLOR with the Abbott logo and a two-letter Abbo-Code designation, DK, in the following packaging sizes:

Bottles of 30 (NDC XXXX-XXXX-XX), ABBO-PAC unit dose strip packages of 100 (NDC XXXX-XXXX-XX), and RAD-PAK™ unit-of-use compliance package of 5 tablets in individual blisters.

**CLINICAL STUDIES****Indication XXX**

In a controlled clinical study of XXX performed in the United States, where significant rates of both penicillin-resistant and macrolide-resistant *Strep. pneumoniae* were observed, ERADOMYCIN was compared to XXX. In this study, very strict evaluability criteria were used to determine clinical response. For the XXX patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was XX% for ERADOMYCIN and XX% for the XXX.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. The following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

<sup>101</sup> 100070 Hepatic study (M99-126)  
<sup>102</sup> 100071 Renal study (TBD)

**Error! Bookmark not defined.U.S. Acute XXX Study  
ERADOMYCIN vs. Comparator XXX**

<b>EFFICACY RESULTS</b>	
<b>PATHOGEN</b>	<b>OUTCOME</b>
<i>S. pneumoniae</i>	ERADOMYCIN success rate, X/X (X%) control X/X (X%)
<i>H. influenzae</i> *	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>M. catarrhalis</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>S. pyogenes</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
Overall	ERADOMYCIN success rate X/X (X%), control X/X (X%)
None of the <i>Strep. pneumoniae</i> isolated pre-treatment was resistant to ERADOMYCIN; X% were resistant to the control agent.	

**Safety:**

The incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the two agents.

In two other controlled clinical trials of indication XXX performed in the United States, where significant rates of penicillin-resistant and macrolide-resistant *Strep. pneumoniae* were found, ERADOMYCIN was compared to XXX. In these studies, very strict evaluability criteria were used to determine the clinical responses. In the XXX patients who were evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was XX% for both ERADOMYCIN and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

**Error! Bookmark not defined.Two U.S. Acute XXX Studies  
ERADOMYCIN vs.  
Comparator XXX**

<b>EFFICACY RESULTS</b>	
<b>PATHOGEN</b>	<b>OUTCOME</b>
<i>S. pneumoniae</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>H. influenzae</i> *	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>M. catarrhalis</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>S. pyogenes</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
Overall	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
Of the <i>Strep. pneumoniae</i> isolated pre-treatment, X% were resistant to ERADOMYCIN and X% were resistant to the control agent.	

**Safety:**

The incidence of adverse events in all patients treated, primarily diarrhea (X% vs. X%) and XXX (X vs. X%)

was clinically and statistically lower in the ERADOMYCIN arm versus the control arm.

#### ANIMAL PHARMACOLOGY AND TOXICOLOGY

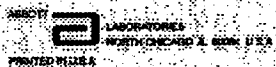
ERADOMYCIN is rapidly and well-absorbed with dose-linear kinetics, low protein binding, and a high volume of distribution. Plasma half-life ranged from 1 to 6 hours and was species dependent. High tissue concentrations were achieved, but negligible accumulation was observed. Fecal clearance predominated. Hepatotoxicity occurred in all species tested (i.e., in rats and monkeys at doses 2 times greater than and in dogs at doses comparable to the maximum human daily dose, based on  $\text{mg}/\text{m}^2$ ). Renal tubular degeneration (calculated on a  $\text{mg}/\text{m}^2$  basis) occurred in rats at doses 2 times, in monkeys at doses 8 times, and in dogs at doses 12 times greater than the maximum human daily dose. Testicular atrophy (on a  $\text{mg}/\text{m}^2$  basis) occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose. Corneal opacity (on a  $\text{mg}/\text{m}^2$  basis) occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose. Lymphoid depletion (on a  $\text{mg}/\text{m}^2$  basis) occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose. These adverse events were absent during clinical trials.

#### REFERENCES

- 1.
- 2.

Filmstab - Film-sealed tablets, Abbott  
TM - Trademark

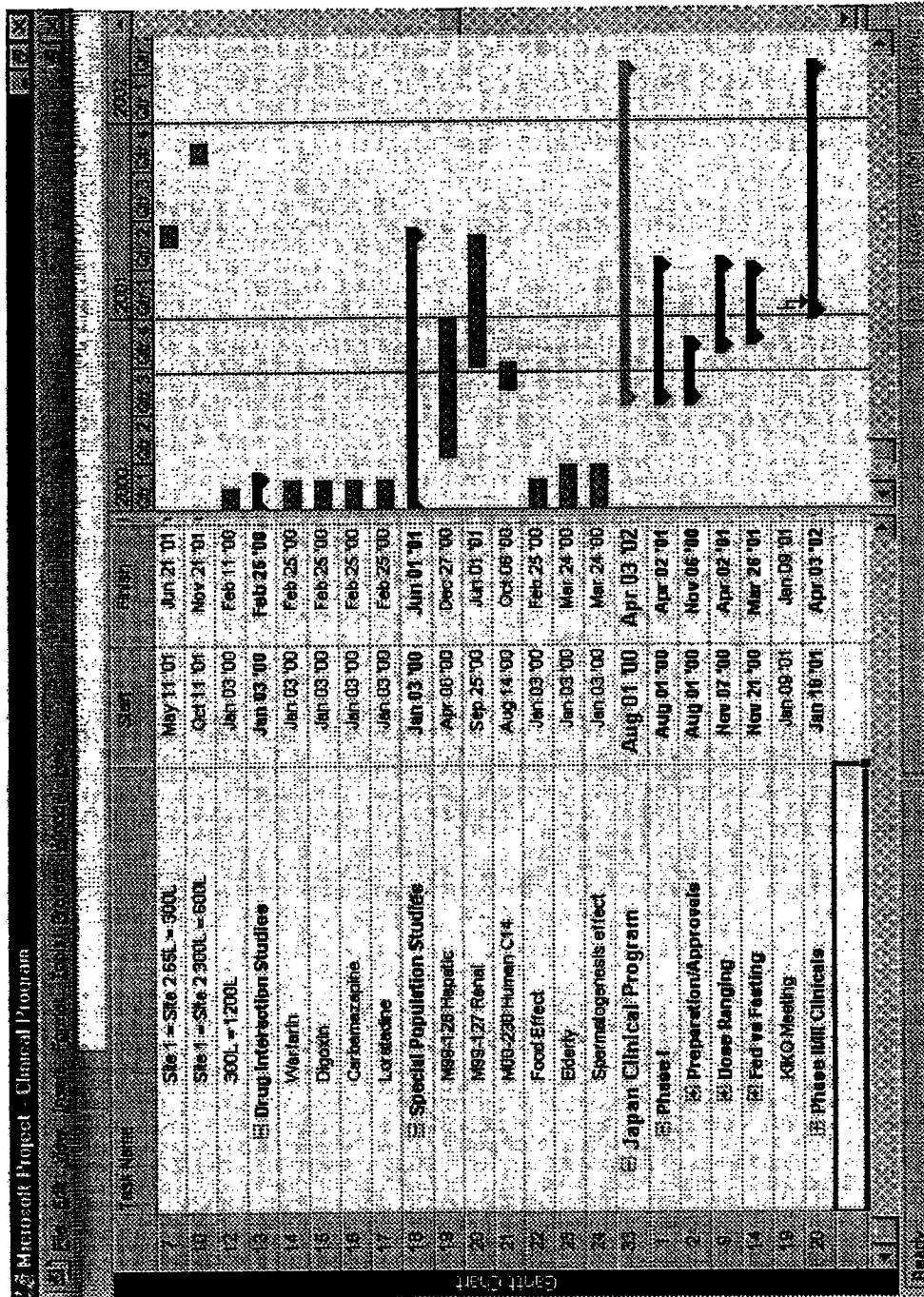
Revised: January, 1997



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Task Name		Start	End	Period
0	5 Clinical Program	Jan 03 '00	Jun 21 '02	
1	5.1 PHASE III	Nov 08 '99	Jun 21 '02	
2	5.1.1 M00-218 CAP 150mg QD vs 150mg BID	Nov 08 '99	Jun 28 '01	
3	5.1.2 M00-225 AMS 150mg QD vs 150mg BID	Nov 08 '99	Jun 28 '01	
4	5.1.3 M00-216 AREC3 vs AZD5363/US	Nov 08 '99	Jun 28 '01	
5	5.1.4 M00-217 AREC3 vs Lapatinib/US	Nov 08 '99	Jun 28 '01	
6	5.1.5 M00-223 A 50 vs Penicillin/US	Nov 08 '99	Jun 28 '01	
7	5.1.6 M00-222 A 50 vs Penicillin/Europe	Nov 08 '99	Jun 28 '01	
8	5.1.7 M00-221 CAP vs Levofloxacin	Sep 03 '01	Jun 21 '02	
9	5.1.8 M00-220 CAP vs TBU Europe	Sep 03 '01	Jun 21 '02	
10	5.1.9 M00-219 AMS vs Augmentin/US	Sep 03 '01	Jun 21 '02	
11	5.1.10 M00-225 AMS vs TBU Europe	Sep 03 '01	Jun 21 '02	
12	5.2 Phase I	Jan 03 '00	Nov 21 '01	
13	5.2.1 Bestudies	Jan 03 '00	Nov 21 '01	
14	5.2.1.1 M99-128 10L vs 7.5L	Jan 14 '00	Feb 24 '00	
15	5.2.1.2 M00-205 45L vs 300L	Sep 25 '00	Nov 03 '00	
16	5.2.1.3 Particle Size TBD	Jan 03 '00	Apr 28 '00	
17	5.2.1.4 Size 1 - Size 2 300L vs 300L	May 11 '01	Jun 21 '01	
18	5.2.1.5 Size 1 - Size 2 300L vs 600L	Oct 11 '01	Nov 21 '01	
19	5.2.1.6 300L vs 1200L	Jan 03 '00	Feb 11 '00	
20	5.2.1.7 Drug Interaction Studies	Jan 03 '00	Feb 28 '00	
21	5.2.1.8 Verfact	Jan 03 '00	Feb 25 '00	
22	5.2.1.9 Dapath	Jan 03 '00	Feb 25 '00	

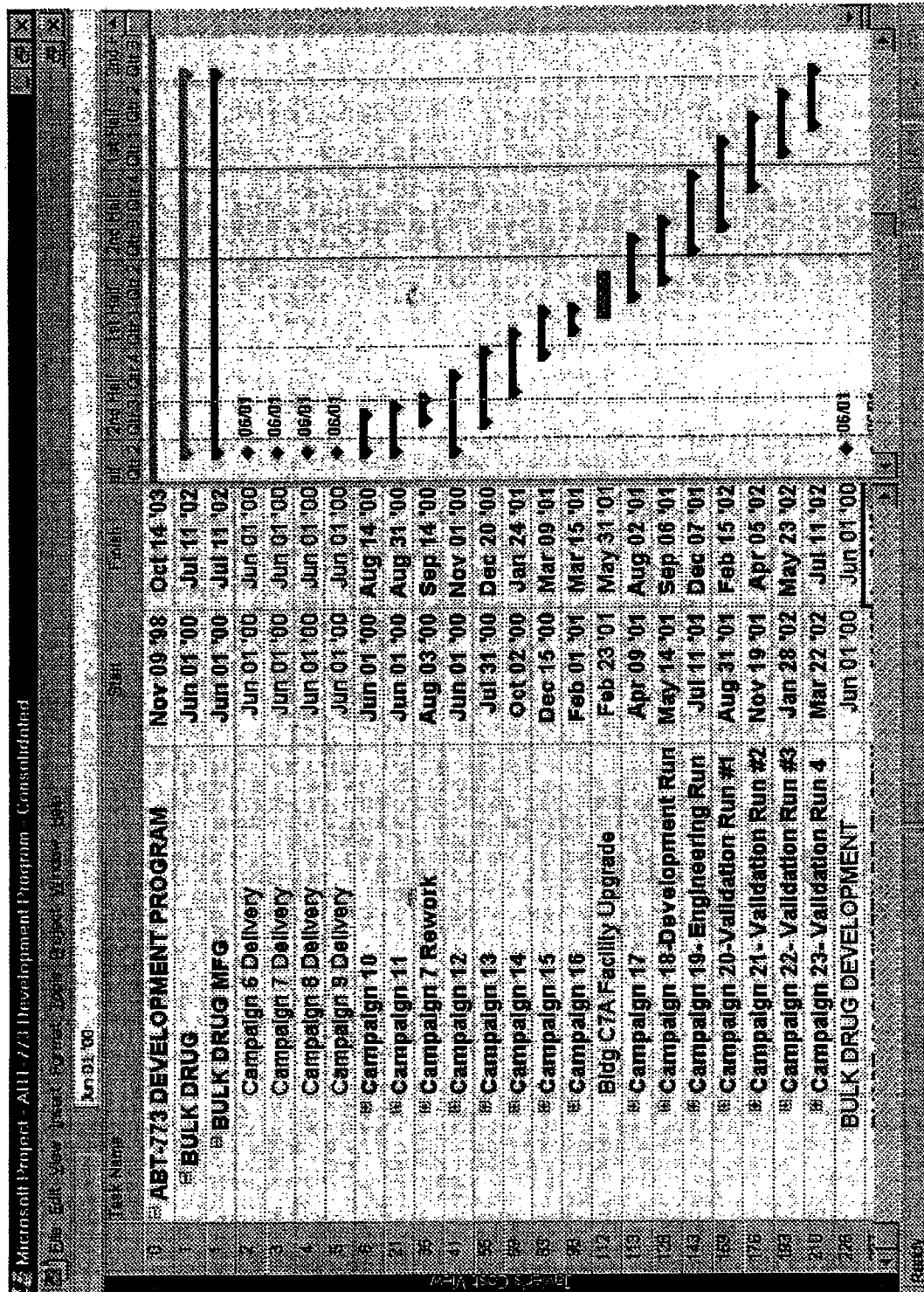




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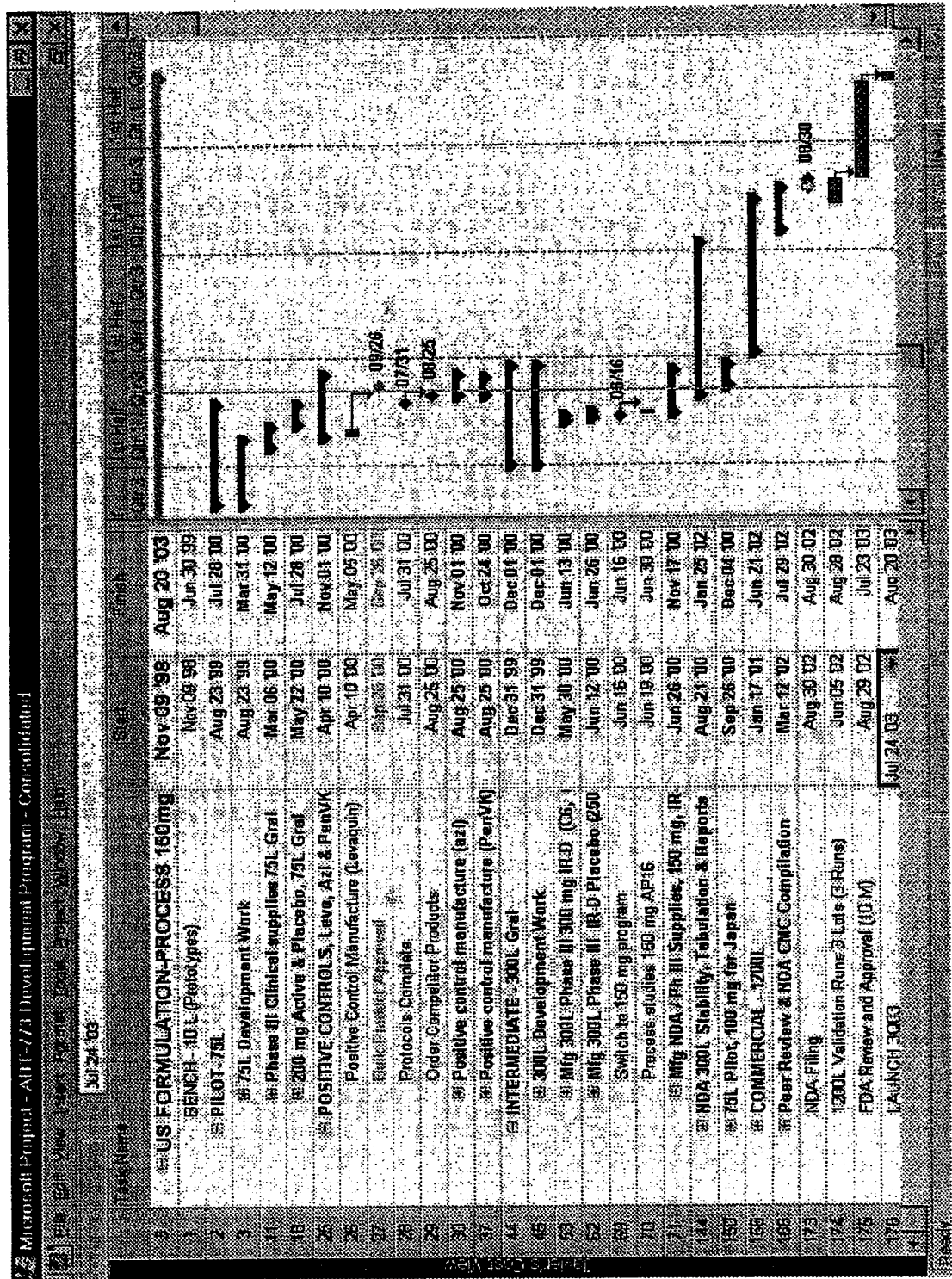
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ABBT205035



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ABBT205036



Microsoft Project - Ex-US Formulation Development

File Edit View Format Tools Project Window Help

Project: Ex-US Formulation Development

Task Name Start Finish

1	EX-US Formulation Development	Mar 16 '00	Aug 29 '02
2	25L Process Verification	Mar 16 '00	Oct 05 '01
3	85 L Process Verification	Oct 18 '00	May 16 '01
4	Site 1 = Site 2 Bio 85J V 300L	Jul 25 '00	May 01 '02
5	800L Process Transfer	Mar 16 '00	Jul 24 '01
6	Site 1 = Site 2 Bio 600L vs 300L	Mar 16 '00	Apr 04 '02
7	Production Batch Analysis	Mar 16 '00	Oct 11 '01
8	Demonstration Batch	Mar 16 '00	Jun 04 '02
9	Registration Filing	Apr 11 '02	Aug 29 '02

Task Name Start Finish

1 EX-US Formulation Development | Mar 16 '00 | Aug 29 '02 |

2 25L Process Verification | Mar 16 '00 | Oct 05 '01 |

3 85 L Process Verification | Oct 18 '00 | May 16 '01 |

4 Site 1 = Site 2 Bio 85J V 300L | Jul 25 '00 | May 01 '02 |

5 800L Process Transfer | Mar 16 '00 | Jul 24 '01 |

6 Site 1 = Site 2 Bio 600L vs 300L | Mar 16 '00 | Apr 04 '02 |

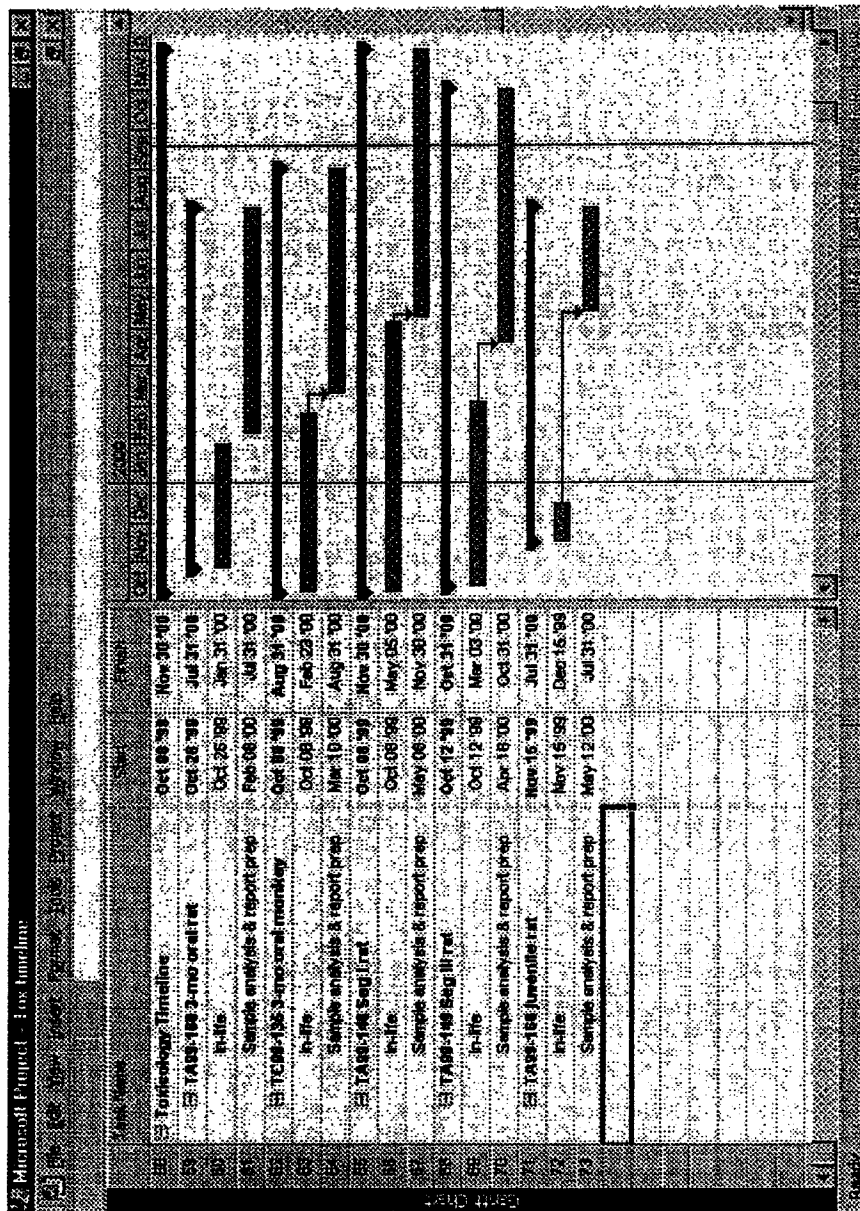
7 Production Batch Analysis | Mar 16 '00 | Oct 11 '01 |

8 Demonstration Batch | Mar 16 '00 | Jun 04 '02 |

9 Registration Filing | Apr 11 '02 | Aug 29 '02 |

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ABBT205037



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ABBT205038

## 5.0 Project History

### 5.1 Expert Strategic Review Process - Summaries

#### 5.2 Highlights re: NCE

- ABT-773 was approved by PPCC in 03/97 for development by the Macrolide Venture. Projected NDA date was 12/00.
- Fifty kg of drug was delivered in 1997. Drug chemistry and cost of drug was a major challenge to development cost and timing. NDA projected date was moved to 03/01 with 50% probability.
- First Phase I study was initiated in Netherlands in 11/97. Based on PK results, the request for a QD ER formulation and no major breakthroughs in chemistry, the NDA projected date was moved to 06/02 with 80% probability.
- All process chemistry efforts and delivery activities were put on hold in 04/98 due to concerns of GI/taste issues with the drug. A comparative safety study using 300mg and 600mg/day of ABT-773 vs Clari 500mg bid was initiated. NDA projected date was moved to 09/02 with 80% probability.
- The encouraging safety results lifted the hold on the process chemistry and delivery activities. For 5 months there were no efforts on process research and delivery activities for drug substance. The first ER prototypes were not acceptable. A Phase IIA study using unformulated capsules was initiated in Europe in ABECB patients by end of 1998. NDA projected date was kept at 09/02 with 80% probability.
- Significant breakthroughs were achieved in bulk drug synthesis and an ambitious development program was initiated by end of 1998 to develop a QD formulation. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen on 8/99 for further development based on pharmacokinetics, safety, and ease of manufacture. The Venture had undertaken a challenging chemistry, formulation and clinical development plan and the NDA projected date had been brought forward to 12/01.
- The Phase 2a study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patient compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen.
- Three Phase 2b studies were started in Sept. 1999 in both the US and EU investigating ABT-773 once daily doses. M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days). M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days). M99-048 - Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)
- Scale-up activities to develop a 300mg tablet were initiated at the 75L pilot scale in 9/99, moving to a 300L intermediate scale in Jan 2000. A bioequivalence study was successful comparing the bench scale clinical lots to the 75L pilot scale lots.

- The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABECB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.
- The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.
- Based on the Phase 2b efficacy and safety results, the decision was made to change the tablet dose from 300mg to 150mg. This decision moved the regulatory filing date forward 8 months to Aug 2002 and postponed the start date of the Phase III clinical studies to Nov 2000, in order to prepare 150mg clinical supplies.
- A Japanese bridging study was conducted in Hawaii to evaluate safety and pharmacokinetics of Japanese and non-Japanese subjects. Over the studied doses (150, 300 and 600 mg single and multiple QD), ABT-773 AUC but not C<sub>max</sub> deviated from dose-proportionality in the Japanese and non-Japanese subjects. At equivalent doses, the Japanese subjects had about 50% greater ABT-773 AUC than the non-Japanese subjects. Based on this result, the Japanese Phase I program will be repeated in Japan. Once Phase I results are available and the clinical agency KIKO has been consulted, the Phase II/III program in Japan will be finalized. It is unknown at this time if a separate Japanese dose will be required.

#### 5.1 Historical Changes to ABT-XXX Target Product Profile

Table 4.0.a Historical Changes to ABT-XXX Target Product Profile		
PPCC/DDC Profile (12/10/97)	Current Profile (9/00)	Rationale for Profile Change
Activity against Gram +, Gram -, atypicals	Activity against Gram +, Gram -, atypicals	No Change
Activity against <i>H. influenzae</i> = azi	Activity against <i>H. influenzae</i> = azi	No Change
Active against 80% of Gram + resistant strains of efflux and MLS-c	Active against 80% of Gram + resistant strains of efflux and MLS-c	No Change
Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	No Change
Maintain balanced plasma/tissue levels similar to clari	Maintain balanced plasma/tissue levels similar to clari	No Change
Incidence of GI side effects=cephalosporins	Incidence of GI side effects=azi	Azithromycin is a more important competitor in the U.S.
Incidence of drug-interactions = clari, no contraindications	Incidence of drug-interactions = clari, no contraindications	No Change
QD dosing adult/tablet	QD dosing adult/tablet	No Change
QD dosing ped OS	QD dosing ped OS	No Change
BID dosing for IV	QD dosing for IV	Current competition is QD
Less painful IV at injection site than clari	Comparable pain at injection site than azi	Azi has less pain than clari.
Less metallic taste for tablet than clari.	Less metallic taste than clari XL	Clari XL now available.

OS equal in taste to cephalosporins	OS equal in taste to Azi, Omnicef	Azi and Omnicef most important comparators.
5-day therapy for most indications; up to 10 days for serious infections. 3 day therapy for pharyngitis.	5-day therapy for most indications	No Change
Bulk drug cost less than \$2500/kg at launch and \$1250/kg 3 years post launch.	COGS > 80% SMM at launch	No Change
Maximum adult dose per day of 1 gram.		No Change
Can be given with or without food.		Food effect study to be repeated with final formulation, current studies indicate better absorption with food.





## **Deposition Exhibit 12**

**P's Exhibit IQ**

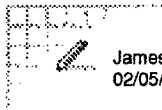


Jeanne M  
Fox/LAKE/PPRD/ABBOTT  
02/14/2001 01:04 PM

To: James Steck/LAKE/PPRD/ABBOTT@ABBOTT  
cc: Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT  
bcc:  
Subject: Re: Studies to Meet Pediatric Rule Requirements

I share your concern and have an even bigger one. In those cases where we are planning to develop an NCE, and we have a target NDA date, I have had difficulty convincing people they have to take the pediatric rule requirements seriously. The answer I keep getting on ABT-773 is "but that project isn't funded". I don't think FDA will buy that answer.

James Steck



James Steck  
02/05/2001 05:20 PM

To: Jeanne M Fox/LAKE/PPRD/ABBOTT@ABBOTT, Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Studies to Meet Pediatric Rule Requirements

Jeanne and Mick

This is just a heads up to let you know that there may be some issues arising in the future about concerns for being able to do studies requested by FDA to meet pediatric rule requirements because these studies "are not funded". Steve and I are running into discussions on this for Depakote ER in migraine where FDA has asked us to do an efficacy study in migraine per the pediatric rule. Of course we will attempt to negotiate with FDA to do the least onerous studies that will still satisfy the pediatric rule requirements, but folks will need to be advised at some point (preferably early on) that meeting this rule is a regulatory obligation and a cost of doing business. I'd appreciate hearing any thoughts you have on this subject.

Jim



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ABBT0568172



## **Deposition Exhibit 15**

**P's Exhibit IM**

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ABT - 773

**Descriptive Memorandum**

*February 2001*

**Abbott Laboratories**

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JH 008153

Descriptive Memorandum: ABT - 773

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**ABT-773****Opportunity Overview**

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase II/III trials. Phase III clinical trials began in Q4, 2000. ABT-773 has an expected U.S. launch date in Q1, 2004. Ex-U.S. launches are projected in 2004 for Europe and Japan.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales.

**The US Market**

The overall antibiotic market in the U.S. reached \$9.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were \$5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped \$2.1 and \$1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of the quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>1995-99</sub>	TRXs (MM)	Share	CAGR <sub>1995-99</sub>
Penicillins	\$148.3	2.6%	-1.0%	62.5	23.7%	-5.6%
Cephalosporins	\$880.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Cefixime	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefadroxil	\$180.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$406.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.5	27.9%	19.9%	36.1	16.3%	20.6%
Clarithromycin	\$890.5	12.1%	8.1%	11.3	5.1%	1.2%
Zithromax	\$691.1	15.8%	42.1%	24.4	11.0%	41.9%
Other	\$14.9	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	\$1,822.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$882.5	15.8%	8.3%	14.1	6.4%	3.1%
Levofloxacin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$180.2	3.3%	-2.2%	3.0	1.3%	-8.4%
Amoxicillin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$580.5	10.3%	-1.1%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	\$5,715.4	100.0%	6.9%	221.5	100.0%	0.1%

*U.S. Market Projections*

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.
- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, evernimomycins, peptides, others).
- Several key branded antibiotics will lose patent exclusivity over the next three to five years. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

*The Ex-U.S. Market*

- Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. Tab/cap represents the largest segment, with sales of \$9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales (\$370MM).

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**Scientific Rationale for ABT-773**

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant Gram + organisms, particularly macrolide-resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

**Clinical Studies**

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
<i>S. pneumoniae</i>	100% (13/13)	90% (9/10)	96% (22/23)
<i>M. catarrhalis</i>	100% (6/6)	100% (7/7)	100% (13/13)
<i>H. influenzae</i>	96% (23/24)	92% (24/26)	92% (47/50)
<i>H. parainfluenzae</i>	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	95% (77/80)	92% (73/79)
Failure	4% (3/80)	8% (6/79)

Clinical and Bacterial Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/24)	0% (0/5)	6.5% (11/168)
Diarrhea	11% (9/84)	0% (0/5)	8% (14/168)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/168)
Dyspnea	2% (2/84)	1% (1/85)	1% (2/168)
Blow Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/168)
Fever		2% (2/85)	1% (2/168)

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The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Doses of 150mg QD, 300mg QD, and 600mg QD were tested. Of the enrolled subjects, 342 were clinically evaluable, and 169 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD	ABT-773 300mg QD	ABT-773 600mg QD	Overall Eradication
<i>S. pneumoniae</i>	83% (10/12)	90% (9/10)	100% (13/13)	91% (32/35)
<i>M. catarrhalis</i>	80% (8/10)	92% (12/13)	91% (10/11)	88% (30/34)
<i>H. influenzae</i>	94% (17/18)	89% (17/19)	83% (19/23)	88% (53/60)
<b>Clinical Response</b>				
Cure	87% (98/113)	90% (105/117)	90% (101/112)	
Failure	13% (15/113)	10% (12/117)	10% (11/112)	
<b>Clinical &amp; Bacteriological Response</b>				
Cure	84% (42/50)	88% (49/56)	94% (59/63)	
Failure	16% (8/50)	12% (7/56)	6% (4/63)	
<b>Adverse Events</b>				
Taste Perversion	5% (4/84)	19% (25/129)	29% (37/129)	17% (66/384)
Diarrhea	13% (16/126)	12% (15/129)	21% (27/129)	15% (58/384)
Nausea	7% (9/126)	13% (17/129)	30% (38/129)	17% (64/384)
Vomiting	2% (3/126)	3% (4/129)	11% (14/129)	5% (21/384)
Nausea & Vomiting	0 (0/126)	<1% (1/129)	4% (5/129)	2% (5/384)
Abdominal Pain	4% (5/126)	4% (5/129)	4% (5/129)	4% (15/384)

The safety and efficacy of ABT-773 in Acute Bacterial Sinusitis (ABS) were studied in a multi-center Phase IIb clinical trial conducted from October 1999 to March 2000. Dosing regimens of 150mg QD, 300mg QD, and 600mg QD were tested. Of the 292 enrolled subjects, 246 were clinically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD	AB T-773 300mg QD	ABT-773 600mg QD	Overall Eradication
<i>S. pneumoniae</i>	3/3	8/8	9/12	20/23
<i>M. catarrhalis</i>	8/9	3/4	4/4	15/17
<i>H. influenzae</i>	3/5	7/7	5/7	15/19
<i>S. aureus</i>	1/1	1/1	3/4	5/5
<b>Clinical Response</b>				
Cure	89% (70/79)	83% (70/84)	71% (59/83)	
Failure	11% (9/79)	17% (14/84)	29% (24/83)	
<b>Adverse Events</b>				
Taste Perversion	1% (16/97)	14% (14/98)	27% (28/97)	14% (41/292)
Diarrhea	6% (6/97)	6% (6/98)	17% (16/97)	10% (28/292)
Nausea	3% (3/97)	12% (12/98)	26% (25/97)	14% (40/292)
Vomiting	1% (1/97)	6% (6/98)	17% (16/97)	8% (23/292)

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The safety and efficacy of ABT-773 in community-acquired pneumonia (CAP) were studied in a multi-center Phase IIIb clinical trial from October 1999 to March 2000. Dosing regimens of 300mg QD and 600mg QD were tested. Of the 187 enrolled subjects, 1248 were clinically evaluable, and 15 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)	91%	(20/22)
<i>M. catarrhalis</i>	75%	(5/8)	50%	(2/4)	67%	(8/12)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)	81%	(22/27)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)	93%	(27/29)
<i>C. pneumoniae</i>	95%	(19/20)	79%	(19/24)	86%	(38/144)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)	100%	(5/5)
<b>Clinical Response</b>						
Cure	92%	(72/78)	80%	(56/70)		
Failure	8%	(6/78)	20%	(14/70)		
<b>Clinical &amp; Bacterial Response</b>						
Cure	92%	(54/59)	82%	(47/57)		
Failure	8%	(5/59)	18%	(10/57)		
<b>Adverse Events</b>						
Taste Perversion	17%	(16/95)	26%	(24/92)	21%	(40/187)
Diarrhea	14%	(13/95)	19%	(17/92)	16%	(30/187)
Nausea	12%	(11/95)	22%	(20/92)	17%	(31/187)
Vomiting	10%	(9/95)	15%	(14/92)	12%	(23/187)

• Appendix 1

Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Torayama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

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